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Toxicological Profile for Creosote

Clement Associates, Inc., Fairfax, VA

Prepared for:

Agency for Toxic Substances and Disease Registry, Atlanta, GA

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The ATSDR Toxicological Profile for Creosote is intended to characterize succinctly the toxicological and health effects information for the substance. It identifies and reviews the key literature that describes the substances's toxicological properties. Other literature is presented but described in less detail. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced. The profile begins with a public health statement, which describes in nontechnical language the substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine the substance's health effects is described. Research gaps in nontoxic and health effects information are described. Research gaps that are of significance to the protection of public health will be identified in a separate effort. The focus of the document is on health and toxicological information.

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, and on October 17, 1990.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by CERCLA, as amended.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about creosote and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Creosote as been found at 31 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for creosote. As EPA evaluates more sites, the number of sites at which creosote is found may change. The information is important for you because creosote may cause harmful health effects and because these sites are potential or actual sources of human exposure to creosote.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as creosote, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS CREOSOTE?

Creosote is a complex mixture of many chemicals. There are three kinds of creosote. One type results from high-temperature treatment of coal (coal-tar creosote), one results from high-temperature treatment of beech and other woods (beechwood creosote), and one comes from the resin of the creosote bush (creosote bush resin). Coal-tar creosote is the most widely used wood preservative in the United States. Coal-tar products are also ingredients in medicines which are used to treat skin diseases. About 300 chemicals have been identified in coal-tar creosote, and there may be 10,000 other chemicals present in the mixture. The major chemicals in coal-tar creosote that can cause harmful health effects are polycyclic aromatic hydrocarbons (PAHs), phenol, and cresols. Beechwood creosote was at one time used as a disinfectant and as a treatment for coughs, but it is rarely used today. The major chemicals present in beechwood creosote are phenol, cresols, and guaiacol. Because coal-tar creosote is the only type found in the environment and hazardous waste sites, its effects on human health will be emphasized in this toxicological profile. Furthermore, because this profile specifically addresses the creosote mixture, effects on health from exposure to the individual major chemicals in creosote, namely, the PAHs or phenol, will not be discussed in any great detail. The Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Polycyclic Aromatic Hydrocarbons and the ATSDR Toxicological Profile for Phenol provide more information on these chemicals.

Coal-tar creosote is usually a heavy, oily, liquid that is typically amber to brown in color. Mixtures of creosote and other coal-tar products are black. The creosote found at hazardous waste sites is most often a black, heavy liquid. It has a sharp smoky odor, and a burning taste. It burns easily, but does not dissolve readily in water.

Creosote does not occur naturally in the environment but it can be released to water and soil through its use as a wood preservative. However, there are many known natural sources for components of the creosote mixture, such as PAHs. For more information on the natural sources of these components, the reader can refer to the ATSDR Toxicological Profile for Polycyclic Aromatic Hydrocarbons. Some parts of the creosote mixture can enter groundwater or change into other substances while other parts persist in treated wood products for decades. More information on the chemical and physical properties of creosote can be found in Chapter 3 and on its occurrence and fate in the environment in Chapters 4 and 5.

1.2 HOW MIGHT I BE EXPOSED TO CREOSOTE?

The major sources of human exposure to coal-tar creosote are contaminated hazardous waste sites, wood treatment facilities, and wood products treated with creosote. You cannot buy coal-tar creosote for treating wood products in your home. Wood products that are typically treated with creosote are railroad ties used by the railroads and for landscaping, telephone poles, marine pilings, and fence posts. You can also be exposed to creosote through contact with soil, water, or air contaminated as the result of releases from waste disposal sites and wood treatment facilities and the burning of treated scrap wood. Exposure of the general population to creosote from currently operating wood treatment facilities should be minimal because all of these facilities are subject to strict controls by the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA). However, exposure to creosote from abandoned wood treatment facilities is possible. There should be very little exposure of the average homeowner to creosote solutions used for wood treatment because it can only be sold to certified applicators, however, you can still be exposed to creosote treated products.

There is no information on background levels of creosote in air or food. Background levels of certain parts of the creosote mixture such as PAHs can be found in some city soils and foods, but it is not known if these substances came from creosote. For more information on human exposure to creosote see Chapter 5.

1.3 HOW CAN CREOSOTE ENTER AND LEAVE MY BODY?

Creosote can enter your body through the lungs as a contaminant of air, through the stomach and intestines after eating contaminated food or drinking contaminated water, or through the skin. Although there is no information on how fast or how much of the creosote mixture is absorbed, many of the parts of the creosote mixture (for example, PAHs) are rapidly absorbed through the lungs and the stomach and the intestines.

The most common routes of exposure around hazardous waste sites are likely to be through the skin, and drinking water contaminated with creosote. Although it is not known how rapidly creosote can enter the body through the skin, creosote can cause reddening just from skin contact. Eating soil contaminated with coal-tar creosote can also provide a source of exposure. Chemicals in coal-tar creosote appear to accumulate in the body, particularly in fat tissue. Most of the chemicals in creosote that are taken into the body and are not stored in the body tissues, leave in the feces within a few days. More information on how creosote enters and leaves the body can be found in Chapter 2.

1.4 HOW CAN CREOSOTE AFFECT MY HEALTH?

Reports describing coal-tar creosote poisoning in workers or accidental or intentional ingestion of coal-tar creosote indicate that brief exposures to large amounts of coal-tar creosote can cause harmful effects on your skin, eyes, nervous system, and kidneys and can result in death. Longer-term exposure to lower levels of coal-tar creosote can also result in damage to your skin, such as reddening, blistering or peeling.

The major organs or systems affected by longer-term exposure to lower levels of coal-tar creosote in animals are the skin and lungs, whereas only the skin has been observed to be affected in humans under these exposure conditions. All of these effects worsen as the level of coal-tar creosote exposure increases.

An increased risk for cancer has been demonstrated in animals exposed to coal-tar creosote. Birth defects have been seen in livestock exposed to coal-tar creosote-treated wood. Since these effects were seen in animals, it is also possible that they could occur in humans. However, we have no information about these effects in humans. More information on the health effects associated with exposure to creosote is presented in Chapter 2.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-1 through 1-4 show that no information is available on specific amounts of creosote in air, water, or food that cause health effects other than death. Coal-tar creosote can cause death to humans and animals if large enough quantities are swallowed. No information is available on the health effects of inhaled creosote.

Skin contact with a few drops of coal-tar creosote irritates and burns the skin and eyes. Coal-tar creosote also makes the skin more sensitive to the effects of the sun. These effects include burning, irritation and swelling.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CREOSOTE?

There is no medical test to determine if you have been exposed to the creosote mixture. However, in your body, chemicals contained in creosote (PAHs) can attach to substances within the body. The presence of PAHs attached to these substances can be measured in body tissues or blood following exposure to creosote. However, this test is still being developed, and it is not known yet how well it works. In addition, chemicals contained in coal-tar creosote and their breakdown products can be measured in the urine of exposed individuals. Tests on the urine are commonly done to determine if a person has been exposed to coal-tar creosote. This test is not routinely available at a doctor's office and would require special equipment for sampling and detection of the compound. Although these tests can confirm that a person has been exposed to chemicals contained in coal-tar creosote, it is not yet possible to use the test results to accurately predict the severity of any health effects that might occur. Furthermore, these tests are not specific for the chemicals contained in coal-tar creosote, and the chemicals measured could have come from exposure to other sources. Additional information on tests for the measurement of creosote in the body is presented in Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has not developed regulatory standards and guidelines to protect people from the potential health effects of exposure to coal-tar creosote in drinking water and food. However, regulatory standards and guidelines in air and water exist for the key individual PAHs and phenols contained in creosote. For more information on the regulations and guidelines for PAHs and phenols, please refer to the ATSDR Toxicological Profiles for Polycyclic Aromatic Hydrocarbons and Phenol. EPA has declared creosote a restricted use pesticide which means that it can only be bought and used by certified applicators and only for those uses covered by the applicator's certification. The EPA has concluded that any release of creosote to the environment in excess of 1 pound should be reported.

TABLE 1-1. Human Health Effects from Breathing Coal-tar Creosote

Levels in air (ppm)	Length of Exposure	Description of Effects
Short-term Exposure (less than or equal to 14 days)		
		The health effects resulting from short-term exposure of humans to air containing specific levels of creosote are not known.
Long-term Exposure (greater than 14 days)		
		The health effects resulting from long-term exposure of humans to air containing specific levels of creosote are not known.

TABLE 1-2. Animal Health Effects from Breathing Coal-tar Creosote

Short-term Exposure (less than or equal to 14 days)		
Levels in air (ppm)	**Length of Exposure**	**Description of Effects**
		The health effects resulting from short-term exposure of animals to air containing specific levels of creosote are not known.
Long-term Exposure (greater than 14 days)		
Levels in air (ppm)	**Length of Exposure**	**Exposure of Effects**
		The health effects resulting from long-term exposure of animals to air containing specific levels of creosote are not known.

TABLE 1-3. Human Health Effects from Eating or Drinking Coal-tar Creosote

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to food containing specific levels of creosote are not known.
Levels in Water (ppm)		The health effects resulting from short-term exposure of humans to water containing specific levels of creosote are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to food containing specific levels of creosote are not known.
Levels in Water (ppm)		The health effects resulting from long-term exposure of humans to water containing specific levels of creosote are not known.

TABLE 1-4. Animal Health Effects from Eating or Drinking Coal-tar Creosote

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
34,000	<24 hours	Causes death in rats
Levels in Water (ppm)		
		The health effects resulting from short-term exposure of animals to water containing specific levels of creosote are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of animals to food containing specific levels of creosote are not known.
Levels in Water (ppm)		
		The health effects resulting from long-term exposure of animals to water containing specific levels of creosote are not known.

The federal government has developed regulatory standards and guidelines to protect workers from the potential health effects of other coal-tar products in air. OSHA has set a legally enforceable limit (threshold limit value, or TLV) of 0.2 mg/m^3 coal-tar pitch volatiles in workroom air to protect workers during an 8-hour shift.

For more information on regulations and advisories for coal-tar creosote exposure, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to creosote. Its purpose is to present levels of significant exposure for creosote based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of creosote and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited.

Estimates of exposure posing minimal risk to humans (MRLs) are made, where data are believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1986a), uncertainties are associated with the techniques. The data on creosote are inadequate to calculate MRLs.

Creosote is a complex mixture of organic substances. It can be derived from three sources: coal-tar distillates (referred to herein as coal-tar creosote), wood (referred to herein as beechwood creosote), and the resin from leaves of the creosote bush (*Larrea*, referred to herein as creosote bush resin). Coal-tar creosote is defined by the American Wood Preserver's Association (1988) as:

> A distillate derived from coal-tar. As used in the wood preserving industry, creosote denotes a distillate of coal-tar produced by the high temperature carbonization of bituminous coal. Creosote consists principally of liquid and solid aromatic hydrocarbons and contains some tar acids and tar bases; it is heavier than water and has a continuous boiling range beginning at about 200°C.

Coal-tar creosote is widely used as a wood preservative, and is the form of creosote found in the environment and hazardous waste sites.

Beechwood creosote consists mainly of phenol, cresols, guaiacol, xylenol, and creosol. It is a colorless or pale yellowish liquid and it has a characteristic smoky odor and burning taste (Miyazato et al. 1981). It had therapeutic applications in the past as a disinfectant and a stimulating expectorant, but it is rarely used today. Though beechwood creosote and coal-tar creosote have some components in common (e.g., phenols), and some of the adverse effects associated with exposure to beechwood creosote may be due to the phenol component, it is not known whether coal-tar creosote will induce these same effects. Furthermore, coal-tar creosote contains PAHs, some of which are carcinogenic, and beechwood creosote does not. Thus, the relevance of health effects data on beechwood creosote to risk associated with exposure to coal-tar creosote is not known.

Creosote bush resin consists of phenolics (e.g., flavonoids and nordihydroguaiaretic acid), neutrals (e.g., waxes), basics (e.g., alkaloids), and acidics (e.g., phenolic acids). The phenolic portion comprises 83%-91% of the total resin. Nordihydroguaiaretic acid accounts for 5%-10% of the dry weight of the leaves (Leonforte 1986). Again, it is not known if the health effects associated with creosote bush resin are due to the phenolic components common to coal-tar creosote or if these effects would be expected to occur following exposure to coal-tar creosote.

The chemical composition of each of these forms of creosote can vary considerably, depending on the source of coal, wood, or plant, and the design and attendant operating conditions (temperature, gas distillation systems, etc.) used to produce the creosote. Throughout this profile, every attempt will be made to specify the characteristics of the creosote under discussion, and indicate which effects may be expected to be common to two or more forms. Furthermore, since the intent of this profile is to discuss the creosote mixture, and even though it is likely that creosote's toxicity is due largely to the major individual components, the PAHs and phenol, the health effects of these individual components will not be discussed in great detail. However, it is understood that the toxicity of the individual components may not be representative of the actual toxicity of the creosote mixture because of the possibility of synergistic and/or antagonistic interactions in the mixture. For more information on the health effects of these components, the reader can refer to the ATSDR Toxicological Profiles for Phenol and Polycyclic Aromatic Hydrocarbons (ATSDR 1989b, 1990).

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to creosote. No deaths were observed in rats exposed to near saturated vapors of coal-tar creosote for one hour (concentration estimated to be less than 0.033 mL/L) (Pfitzer and Gross 1964). The exposed animals showed signs of slight eye and nose irritation and slight dyspnea. All rats were reported to exhibit weight gains comparable to the control animals and there were no treatment-related lesions observed at necropsy.

No studies were located regarding the following health effects in humans or animals following inhalation exposure to creosote.

2.2.1.2 Systemic Effects

2.2.1.3 Immunologic Effects

2.2.1.4 Neurologic Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

No mutagenic activity was detected in the urine samples of workers briefly exposed to coal-tar creosote vapors in a wood preserving factory (Bos et al. 1984a). The frequency and level of exposure to creosote vapors was not reported. Of the three workers tested, two moved wood in and out of the wood impregnating cylinder and one operated the cylinder. All had the potential for brief inhalation exposure to creosote. Furthermore, the possibility of dermal exposure by contact with residual surface creosote cannot be excluded. The absence of mutagens in the urine samples tested by *Salmonella typhimurium* assay was attributed by the authors to a relatively low level of exposure, improper timing for urine sample collection, and the insensitivity of the assay. The data are not sufficient to draw a conclusion regarding the genotoxic potential of inhaled creosote vapors in humans.

No studies were located regarding genotoxic effects in animals following inhalation exposure to creosote.

2.2.1.8 Cancer

Cases of multiple myeloma were compared in a Swedish case-referent study on past occupational and radiation exposure (Flodin et al. 1987). Exposure was assessed by means of a questionnaire mailed to the study subjects that asked questions concerning occupational exposures (including exposure to coal-tar creosote) and radiation exposure. Radiation exposure included estimates of natural background levels and estimates from medical procedures. The exposure to gamma radiation, either through occupation, medical testing, or from background sources found in building materials, was not significantly associated with an increase in multiple myeloma. A significant crude rate ratio for occupational exposure to coal-tar creosote was obtained (6.0; $p=0.001$). The rate ratio point estimate for occupational exposure to creosote increased to 9.5 after stratifying for age. This result indicates an association between occupational creosote exposure and the subsequent development of multiple myeloma. This study was limited by the number of smokers in the case group as compared with the referent group, by gender differences between the cases and referents, and, possibly, by recall bias and incomplete case ascertainment. Furthermore, it is assumed that the exposure route was primarily dermal, although some inhalation exposure may have been possible. This study does suggest an area for further research, indicating a possible relationship between creosote exposure and the development of multiple myeloma.

Creosote does contain mutagenic PAHs, and therefore an association between creosote exposure and the development of multiple myeloma appears to be biologically feasible. Furthermore, creosote exposure has been associated with cancers of the nasal cavity, larynx, lung, skin, and scrotum (Fraumeni 1975). See Section 2.2.3.8, "Dermal Exposure, Cancer" for a more detailed discussion of the types of cancer associated with exposure to creosote in humans.

No definitive inhalation carcinogenicity bioassays have been conducted with creosote in animals.

2.2.2 Oral Exposure

Figure 2-1 and Table 2-1 describe the health effects observed in laboratory animals associated with oral exposure levels to coal-tar and beechwood creosote at varying time and exposure levels. Although beechwood creosote, creosote bush resin, and coal-tar creosote have some components in common (e.g., phenols), and some of the adverse effects associated with exposure to beechwood creosote may be due to the phenol component (e.g. acute and/or subacute toxicity), it is not known whether coal-tar creosote will induce these same effects. Furthermore, coal-tar creosote contains a complex mixture of carcinogenic/co-carcinogenic PAHs that probably account for the cancer risk associated with chronic exposure, and the other forms of creosote do not.

2.2.2.1 Death

A 70-year-old man died following ingestion of an unspecified amount of "industrial" creosote (presumably coal-tar creosote) (Bowman et al. 1984). Death was attributed to multi-organ failure and occurred 30 hours after admission to the hospital. It is not known if this man had a history of prior creosote ingestion. Death has been reported to occur in adults and children 14 to 36 hours after the ingestion of about 7 g or 1-2 g coal-tar creosote, respectively (Clayton and Clayton 1981). The latter anecdotal information is of limited value because it was obtained from a secondary source that provided no supporting documentation. Thus, ingestion of creosote can be fatal to humans, but the dose level required to produce death cannot be accurately estimated from these reports.

Cases of lethal poisoning resulting from ingestion of large amounts of coal-tar creosote have been reported in larger farm animals. The acute fatal dose for sheep is 4-6 g/kg and for calves, over 4 g/kg (HSDB 1988). The oral LD_{50} for coal-tar creosote is reported to be 433 mg/kg in the mouse and 725 mg/kg in the rat (RTECS 1981). However, another study reported an acute oral LD_{50} of 1700 mg/kg in the rat (Pfitzer and Gross 1964). The reasons for this discrepancy in LD_{50} values are not known. Based on these data, coal-tar creosote can be classified as mildly to moderately toxic.

The acute toxicity of beechwood creosote in both rats and mice was studied following the administration of single gavage doses in a 10% aqueous solution (Miyazato et al. 1981). The oral LD_{50} of beechwood creosote in rats was 870 mg/kg (females) and 885 mg/kg (males). The highest dose at which no death occurred was 600 mg/kg. There was no significant difference between

TABLE 2-1. Levels of Significant Exposure to Creosote - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect)		Reference	Form
						Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE									
Death									
1	Rat	(G)	1 d 1x/d				1700[a] (LD50)	Pfitzer and Gross 1964	coal
2	Rat	(G)	1 d 1x/d		600		M:885 (LD50) F:870 (LD50)	Miyazato et al. 1981	beech
3	Mouse	(G)	1 d 1x/d		M:376 F:313		M:525 (LD50) F:433 (LD50)	Miyazato et al. 1981	beech
Systemic									
4	Rat	(G)	1 d 1x/d	Gastro		2.52 (hyperemia, distension of stomach)		Pfitzer and Gross 1964	coal
Neurological									
5	Rat	(G)	1 d 1x/d				600 (convulsions)	Miyazato et al. 1981	beech
6	Mouse	(G)	1 d 1x/d				313 (convulsions)	Miyazato et al. 1981	beech
INTERMEDIATE EXPOSURE									
Death									
7	Rat	(F)	3 mo 7d/wk		M: 1224 F: 768			Miyazato et al. 1981	beech
8	Mouse	(F)	3 mo 7d/wk		M: 1810 F: 1570			Miyazato et al. 1981	beech
Systemic									
9	Rat	(F)	3 mo 7d/wk	Hemato		M:257 F:163 (decreased red blood cell, increased serum cholesterol)		Miyazato et al. 1981	beech

TABLE 2-1 (Continued)

Figure Key	Species		Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference	Form
				Hepatic		M:257 F:215 (increased liver weight:body weight ratio)			
				Renal		M:317 F:163 (increased kidney weight:body ratio)			
				Other		M: 1224 F:768 (decreased body weight and food intake)			
				Other		M: 1224 (increased spleen body weight ratio)			
10	Mouse	(F)	3 mo 7d/wk	Hemato	M: 1810 F: 1570			Miyazato et al. 1981	beech
				Hepatic		F:345 (increased liver weight:body weight ratio)			
				Renal		M:765 (decreased kidney weight)			
				Other		M: 1810 F: 1570 (decreased body weight and food intake)			
Neurological									
11	Rat	(F)	3 mo 7d/wk			M:257 (increased brain weight:body weight ratio)		Miyazato et al. 1981	beech
Reproductive									
12	Rat	(F)	3 mo 7d/wk			M: 1224 (increased testis: body weight ratio)		Miyazato et al. 1981	beech
CHRONIC EXPOSURE									
Death									
13	Rat	(F)	96 wk 7d/wk				M:313 (death)	Miyazato et al. 1984b	beech

TABLE 2-1 (Continued)

Figure Key	Species		Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect)		Reference	Form
						Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic									
14	Rat	(F)	96 wk 7d/wk	Hemato		M:143 (increased serum F:179 cholesterol)		Miyazato et al. 1984b	beech
				Hepatic		M:143 (increased liver weight:body weight ratio)			
				Renal		M:143 (increased kidney F:179 weight:body weight ratio; increased BUN (male) nephrosis (male) (decreased food intake)			
				Other	M:313 F:394	M:313 (decreased body F:394 weight)			
15	Mouse	(F)	52 wk 7d/wk	Resp		M:247 (histopath) F:297		Miyazato et al. 1984a	beech
				Hemato	M:474 F:532				
				Hepatic		F:297 (increased liver weight:body weight ratio)			
				Renal	F:297	(increased kidney weight:body weight ratio)			
				Other		M:247 (decreased body F:297 weight and food intake)			
Neurological									
16	Rat	(F)	96 wk 7d/wk			M:143 (increased brain F:394 weight:body weight ratio)		Miyazato et al. 1984b	beech
17	Mouse	(F)	52 wk 7d/wk			F:297 (increased brain weight:body weight ratio)		Miyazato et al. 1984a	beech

[a]Converted to an equivalent concentration in food for presentation in Table 1-4.

mg/kg/day = milligrams per kilogram per day; d = day; mo = month; x/d = times per day; (G) = gavage; (F) = feed; NS = not specified; Gastro = gastrointestinal; Hemato = hematological; Resp = respiratory; BUN = blood urea nitrogen; LD50 = lethal dose, 50% kill; beech = beechwood; M = male; F = female.

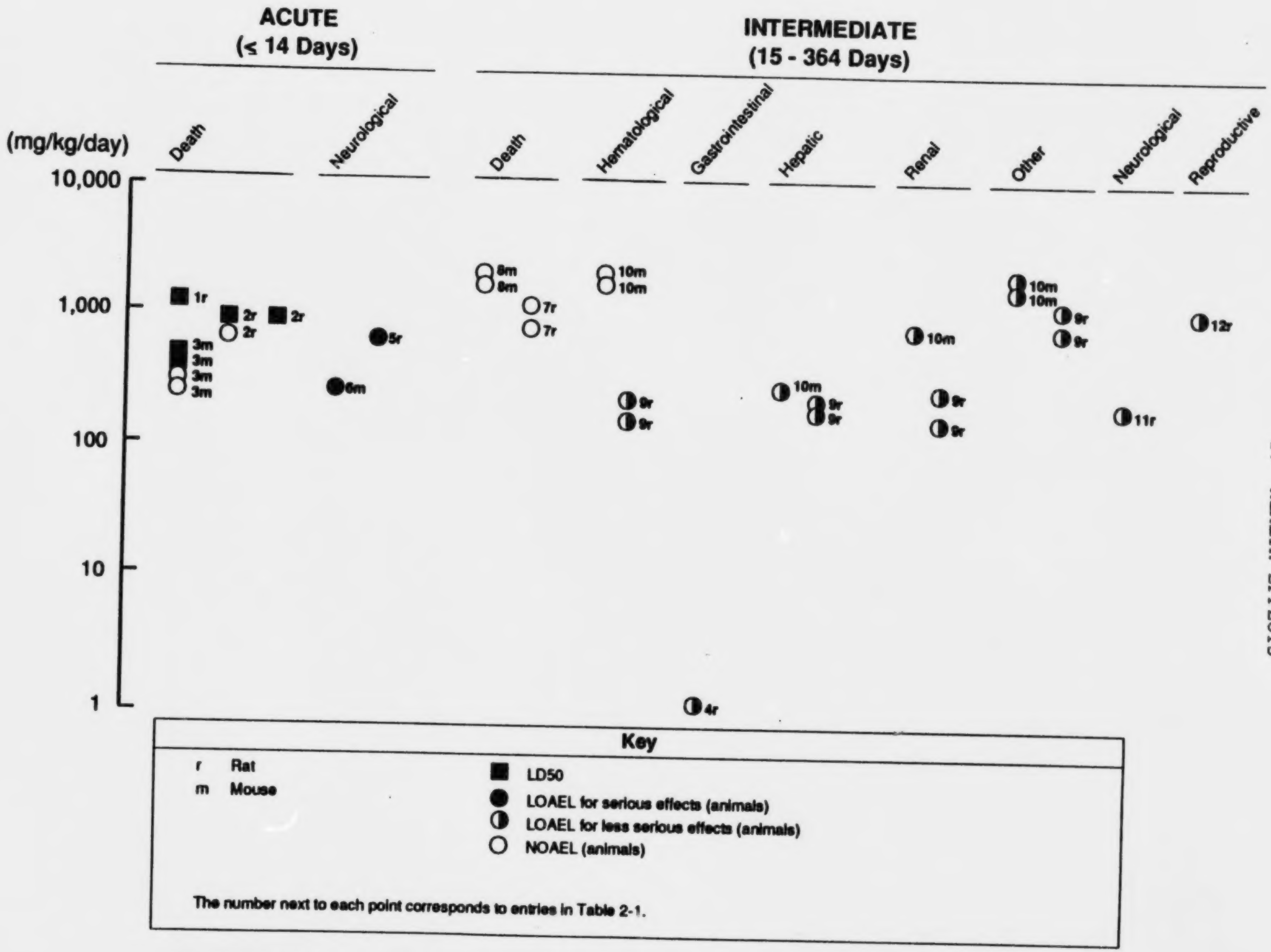

FIGURE 2-1. Levels of Significant Exposure to Creosote - Oral

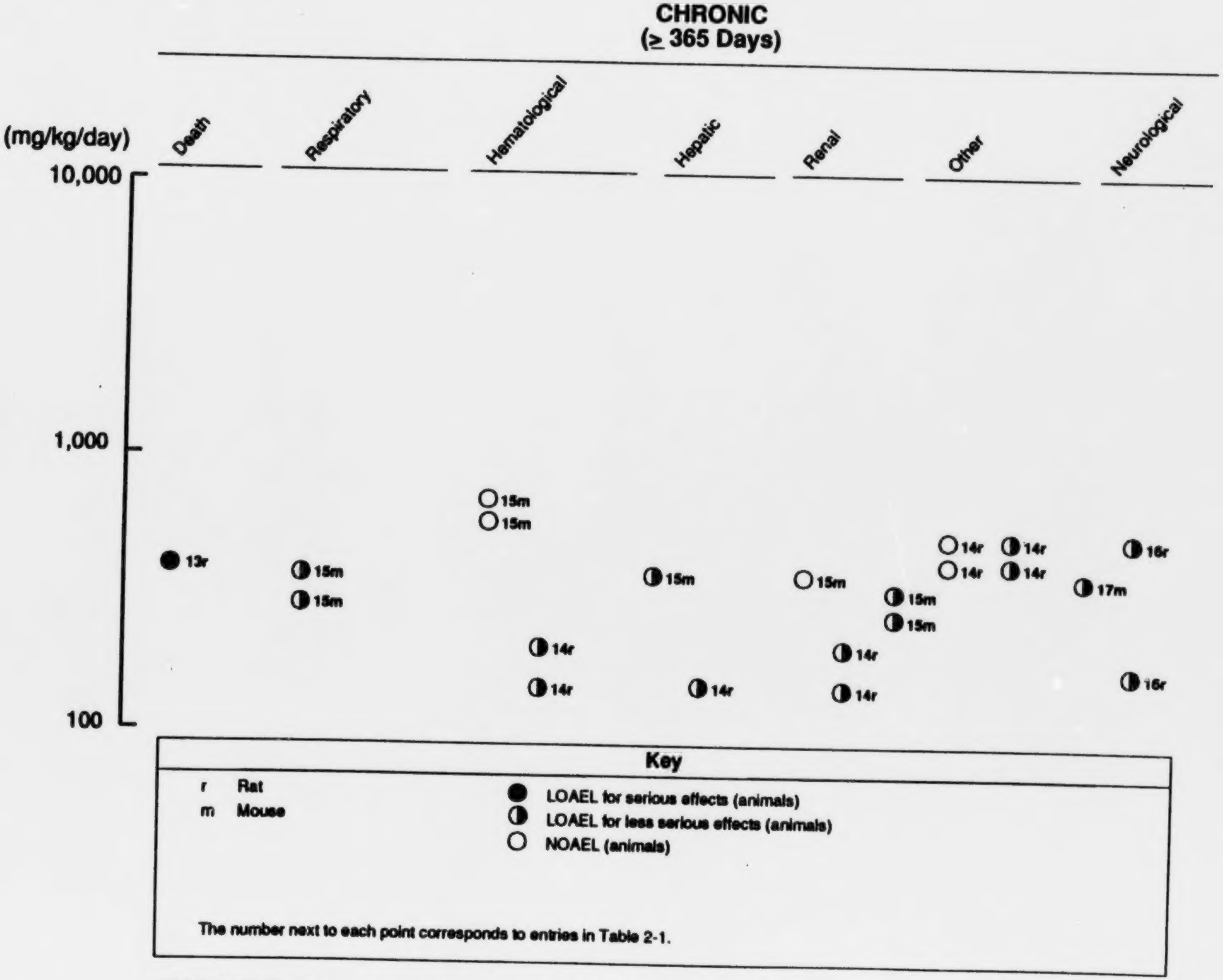

FIGURE 2-1. Levels of Significant Exposure to Creosote - Oral (Continued)

male and female rats with respect to mortality, and most animals died within 30 minutes following severe convulsions. Mice appeared to be more susceptible to the lethal effects of beechwood creosote. The oral LD_{50}s in mice were 433 mg/kg (female) and 525 mg/kg (male). The highest dose at which no death occurred was 313 mg/kg (female) and 376 mg/kg (male). The mortality in female mice was significantly higher than in male mice. Most animals died within 30 minutes following severe convulsions. These results indicate that the acute toxicity of beechwood creosote is relatively low, and some species and sex differences exist.

The highest NOAEL values and all LD_{50} values for death in each species are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.2 Systemic Effects

There is relatively little information available regarding the systemic effects of ingested creosote. The database consists primarily of old anecdotal reports or animal studies that would be considered inadequate by current standards. Three recent studies published by Miyazato et al. (1981, 1984a,b) that evaluated the acute, subchronic, and chronic effects of beechwood creosote in rats and mice comprise the bulk of reliable information on the systemic effects of ingested creosote. Based on the results of these studies, the liver, kidney, and central nervous system may be target organs of creosote toxicity. Effects have also been observed in the gastrointestinal system, respiratory system, and cardiovascular system. No studies were located regarding musculoskeletal or dermal/ocular effects in humans or animals after oral exposure to creosote.

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to creosote.

A slightly higher incidence of bronchitis or thickening of the tracheal mucous membrane was observed in mice who ingested feed that contained 0.3% (equivalent to 247 mg/kg/day for males and 297 mg/kg/day for females) and 0.6% (equivalent to 474 mg/kg/day for males and 532 mg/kg/day for females) beechwood creosote for 52 weeks (Miyazato et al. 1984a). The authors attributed this to irritation from long-term inhalation exposure to volatile components of creosote in the feed, and not a direct toxic effect on the respiratory tissue. These values are presented in Table 2-1 and plotted in Figure 2-1.

Beechwood creosote has been and continues to be used therapeutically on a limited basis as an expectorant/cough suppressant based on its presumed ability to increase the flow of respiratory fluids. The efficacy of creosote (type not specified, but presumably beechwood creosote) as an expectorant was studied by measuring the output of respiratory tract fluids in cats given a single dose of 0.1 or 5 mL/kg (concentration not specified) (Stevens et al.

1943). Creosote produced a slight increase in the output of respiratory tract fluid under these conditions. This is not considered a toxic effect. Given the limitations of this study (e.g., no dose information, no other respiratory effects evaluated), it provides no useful information on the potential respiratory effects of beechwood creosote.

Cardiovascular Effects. The case of a 52-year-old woman who had been taking creosote (type and dose not specified) for 9 years to treat chronic bronchitis was reported by Robinson (1938). The woman was found to be weak, dizzy, light-headed, and hypertensive (blood pressure = 206/140). A modified diet and diuretic therapy relieved all of these symptoms. Upon reinstitution of creosote therapy, her blood pressure rose to 235/130. The author concluded that creosote was responsible for the woman's hypertension. This study provides anecdotal evidence of creosote-induced cardiovascular effects, but the limited sample size, lack of detail on exposure, and possibility of confounding factors limits its usefulness.

No studies were located regarding the cardiovascular effects in animals following oral exposure to creosote.

Gastrointestinal Effects. Ulceration of the oropharynx and petechial hemorrhages over the gastrointestinal serosal surfaces were noted at autopsy in the case of a 70-year-old man who died following ingestion of industrial creosote (Bowman et al. 1984). However, the esophagus and stomach were intact. The authors attributed these effects to acute tissue damage resulting from phenol-induced corrosive effects (phenol is a component of creosote).

Animals that died following the administration of single gavage doses of coal-tar creosote in an acute range-finding study (doses ranged from 2.52-5.00 mg/kg) exhibited hyperemia and distention of the stomach upon necropsy. No studies were located regarding gastrointestinal effects in animals following intermediate- or chronic-duration oral exposure to creosote.

Hematologic Effects. No studies were located regarding hematologic effects in humans following oral exposure to creosote.

Various serum chemistry and hematological parameters were measured by Miyazato et al. (1981, 1984a,b) in rats and mice fed beechwood creosote in the daily diet for 3 months, 52 weeks (mice) or 96 weeks (rats). No significant treatment-related changes were noted in mice of either sex fed up to 1,570 (female) or 1,810 (male) mg/kg/day for 3 months (Miyazato et al. 1981). These doses are considerably higher than the oral LD_{50}s reported for mice by the same authors. One possible explanation for this discrepancy is that the LD_{50}s were determined by bolus gavage injections and in the subchronic study, the beechwood creosote was administered in the feed. A slight reduction in red blood cells (RBCs) and a slight increase in serum cholesterol was noted in male and female rats following dietary exposure to 163 (female) or 257 (male) mg/kg/day and higher for 3 months (Miyazato et al. 1981). The reduction in RBCs was not dose-dependent and was therefore not considered to be toxicologically significant; the significance of the cholesterol changes is not known.

Increases in serum cholesterol were also noted in rats exposed to creosote in the diet for 96 weeks at doses of 143 (male) and 179 (female) mg/kg/day and above (Miyazato et al. 1984b). Chronic (52 weeks) dietary exposure of mice to beechwood creosote resulted in statistically significant dose-related differences in mean cell volume, mean corpuscular hemoglobin, and absolute lymphocyte and neutrophil counts when compared to the corresponding control values. These changes were not considered by the authors to be toxicologically significant; they claimed that the values were within normal physiological ranges (Miyazato et al. 1984a).

The highest NOAEL values and all reliable LOAEL values for hematological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Hepatic Effects. Degeneration and necrosis of hepatocytes were observed at autopsy in the case of a 70-year-old man who ingested "industrial" creosote (Bowman et al. 1984). Given the advanced age of this man and the lack of comparison data, it is not possible to definitively attribute these effects to creosote ingestion.

Liver-to-body-weight ratios tended to increase in rats and mice exposed to beechwood creosote in the diet for either 3 months (rats and mice), 52 weeks (mice) or 96 weeks (rats) (Miyazato et al. 1981, 1984a,b). However, this response is of questionable toxicological significance, since no treatment-related changes were noted during histopathological evaluation. A significant increase in serum glutamic-oxaloacetic transferase (GOT) and glutamic-pyruvic transferase (GPT) levels was also observed in the chronically exposed female mice, but these levels were still within normal physiological range. Taken together, these early changes indicate that if increased doses of beechwood creosote are used, more clear cut hepatotoxic effects would be expected to occur. However, the liver weight changes observed may simply reflect pharmacological changes (e.g., response to enzyme induction).

All reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Renal Effects. A 70-year-old man who ingested a fatal dose of "industrial" creosote became acidotic and anuric before he died, indicating the possibility of kidney failure (Bowman et al. 1984). Acute renal tubular necrosis was revealed at necropsy. However, the acute tubular necrosis may have been due to vascular insufficiency rather than a direct toxic effect on the kidney.

Kidney-to-body-weight ratios tended to increase in rats and mice exposed to beechwood creosote in the diet for either 3 months (rats and mice), 52 weeks (mice) or 96 weeks (rats) (Miyazato et al. 1981, 1984a,b). However, this response is of questionable toxicological significance in the subchronically treated mice and rats of both sexes and the chronically treated female rats since no treatment-related changes were noted at histopathological evaluation. Blood urea nitrogen and serum inorganic phosphorus were elevated in the chronically treated male rats, which is indicative of uremia. Chronic nephrosis, which occurs spontaneously in old male rats, was also observed at a higher incidence in the chronically treated male rats than in the control male rats, and most likely accounts for the biochemical changes observed. The authors concluded that long-term exposure to beechwood creosote accelerated the occurrence of chronic nephrosis in male rats (Miyazato et al. 1984b). These results suggest that beechwood creosote has the potential to induce adverse effects in the kidney.

All reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.3 Immunological Effects

No studies were located regarding immunologic effects in humans or animals following oral exposure to creosote.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to creosote.

The first sign of poisoning following the gavage administration of single high doses (doses not specified) of beechwood creosote to mice and rats was muscle twitching followed by convulsions within 1 to 2 minutes. This was followed by asphyxiation, coma, and death (Miyazato et al. 1981).

Several cases of acute poisoning in cattle have been attributed to ingestion of coal-tar creosote. Six cattle believed to have licked creosote-treated electrical light poles as evidenced by burning over the mucosa of the mouth, tongue, and lips showed the following symptoms: extremely rapid respiration, contracted pupils, cold skin, apparent severe pain, and coma (Hanlon 1938). However, the possibility exists that some of these effects may have been due to ingestion of pentachlorophenol. Pentachlorophenol, like creosote, is an oil-borne wood preservative with extensive use in the public utility industry for treatment of utility poles. Some of the effects observed by Hanlon (1938) are more compatible with the metabolic effects (i.e., uncoupling of phosphorylative oxidation) associated with pentachlorophenol (for more information on the effects of pentachlorophenol, please refer to the ATSDR Toxicological Profile for Pentachlorophenol, ATSDR 1989a). Thus, it is not possible to determine conclusively whether creosote is toxic to the central nervous system of animals based on this report.

Dose-related increased brain-to-body-weight ratios were observed in male rats exposed to beechwood creosote in the diet for 3 months (Miyazato et al. 1981), female mice exposed for 52 weeks (Miyazato et al. 1984a) and male and female rats exposed for 96 weeks (Miyazato et al. 1984b). This response is of questionable toxicological significance because of the lack of a dose-response trend and/or the lack of treatment-related pathological findings at necropsy.

All reliable LOAEL values for neurological effects for each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following oral exposure to creosote.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to creosote. An increase in relative testis weight was observed in rats administered 1,224 mg/kg/day beechwood creosote in the diet for 3 months (Miyazato et al. 1981). There were no accompanying gross or histopathological lesions of the testes in these animals.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following oral exposure to creosote.

2.2.2.8 Cancer

No studies were located that dealt directly with an association between cancer and ingested creosote in humans. Excess cases of breast cancer have been observed in St. Louis Park, Minnesota that were tentatively associated with coal-tar creosote contamination of the water supply. Coal-tar creosote-derived PAHs were first detected in the water supply of St. Louis Park in November 1978, but may have been there for decades. A 100 acre plot of creosote-contaminated soil upon which stood a plant that used creosote and operated from 1917-1972 is believed to be the source of contamination. The levels of creosote or creosote-derived PAHs in the contaminated drinking water of St. Louis Park were not specified. There were 113 cases of breast cancer in St. Louis Park compared to 78 cases in the metropolitan Minneapolis-St. Paul area during 1969 to 1971. An attempt was made to demonstrate that these excess cases could be explained by known risk factors for breast cancer, such as age at first birth, parity, age at menarche and menopause, body mass index, history of benign breast disease, and familial history and had no association with environmental exposure variables (Dean et al. 1988). The authors presented a method to adjust the breast cancer morbidity in St. Louis Park using data from a larger population with documented risk factors for breast cancer ("standard population"). These more stable rates based on breast cancer risk factors were determined in a larger study conducted by Helmrich et al. (1983). Dean et al. (1988) determined that the attributable risk due to the risk factors was higher for the breast cancer cases in St. Louis Park (0.598) than in the metropolitan Minneapolis-St. Paul area (0.311). They then used these attributable risks to calculate an adjusted morbidity ratio to estimate expected numbers of breast cancer cases in the community. After this adjustment, there appeared to be a higher expected number of breast cancer cases (n=134) than the observed number (113) in St. Louis Park, thereby negating any association with creosote in the water supply. It is necessary when using any standardization method in adjusting rates to ensure comparability among the groups in the study population that are being compared and between the study population and the standard population. It would appear that differences do exist between women in St. Louis Park, the metropolitan Minneapolis-St. Paul area, and the larger cohort studied by Helmrich et al. (1983). These differences were not thoroughly examined by Dean et al. (1988) and could include differences in demographic, economic, and/or environmental factors. However, Dean et al. (1988) did note a difference in religious backgrounds between the study population described by Helmrich (1983) and that of the St. Louis Park area. These dissimilarities indicate that the populations are not directly comparable and therefore the adjustment of rates is not appropriate. The authors did not attempt to incorporate creosote contamination of the water as an independent variable in their analysis.

The Minnesota Department of Health (1985) also reviewed the St. Louis Park data and concluded that this study did not provide adequate evidence to associate breast cancer with creosote-contaminated groundwater. They supported this conclusion with the following observations. It is not possible to classify individuals or residences within St. Louis Park according to their relative degree of historical exposure to PAH contaminants in drinking water because the pattern and history of municipal well contamination are not known; contaminant levels were measured at the well head and not at the tap; water treatment, storage, and distribution effects on contaminant concentration are not known; and much of the water distribution system is lined with coatings made of coal-tar or asphalt. Furthermore, given the ubiquitous nature of PAHs, it is probable that exposures to PAHs from food would significantly exceed exposures from contaminated St. Louis Park well water. In addition, it was found that the specific PAHs that have been shown to induce mammary tumors in rodents were either not present in contaminated wells or were detected very rarely even in the most highly contaminated wells, and the many published case-control and cohort studies of breast cancer have not demonstrated clear-cut evidence of an association between breast cancer and smoking, which is a significant source of exposure to PAHs. These studies have also identified a number of risk factors that account for some of the observed variations in rates among different groups of women, and the women of St. Louis Park differ from those in the general Metro area with respect to several of the factors that are known to influence breast cancer rates.

Dietary exposure of male and female mice to beechwood creosote at concentrations up to 532 mg/kg/day (which induced signs of toxicity) for 52 weeks induced no treatment-related increase in the incidence of tumors (Miyazato et al. 1984a). This study is limited in that 52 weeks may not be a sufficient treatment duration to observe an increase in the incidence of tumors in mice. However, these same authors reported that dietary exposure of male and female rats to 394 mg/kg/day beechwood creosote (which induced signs of toxicity) for 96 weeks also failed to result in any treatment-related increase in the incidence of tumors (Miyazato et al. 1984b). Based on these results, there is no evidence that ingested beechwood creosote is carcinogenic to mice or rats.

2.2.3 Dermal Exposure

Table 2-2 describes the health effects observed in laboratory animals associated with dermal exposure to coal-tar creosote. Coal-tar creosote exerts its toxic effects primarily via dermal exposure. Several reports were found which describe the occurrence of dermal and ocular irritation, burns, and "warts" (i.e. squamous papillomas) following acute or prolonged skin contact with coal-tar creosote. Coal-tar creosote also induces phototoxicity of the skin, and has been demonstrated to be a skin carcinogen in animals.

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to creosote. The dermal LD_{50} in rabbits has been estimated to be greater than 7.95 g/kg following a 24-hour application of coal-tar creosote to both intact and abraded skin (Pfitzer and Gross 1964).

2.2.3.2 Systemic Effects

The skin is the target organ for creosote toxicity following dermal exposure. No studies were located regarding respiratory, cardiovascular, hematologic, musculoskeletal, hepatic, or renal effects in humans or animals following dermal exposure to creosote.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to creosote. Rabbits that died following single dermal applications of undiluted coal-tar creosote exhibited hyperemia of the intestines (Pfitzer and Gross 1964).

Dermal/Ocular Effects. Burns and irritation of the skin and eyes are the most frequent manifestations of coal-tar creosote toxicity following

TABLE 2-2. Levels of Significant Exposure to Creosote - Dermal

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL	LOAEL (Effect)		Reference	Form
					Less Serious	Serious		
ACUTE EXPOSURE								
Death								
1	Rabbit	1 d 1x/d				> 7.95 g/kg (LD50)	Pfitzer and Gross 1964	coal
Systemic								
2	Mouse	7-21 d 7d/wk 1x/d	Derm		5% in (irritation) paraffin		Wrench and Britten 1975	coal
INTERMEDIATE EXPOSURE								
Cancer								
3	Mouse	8 mo 2x/wk	Derm			0.25ml (CEL)	Roe et al. 1958	coal
4	Mouse	44 wk 2x/wk	Derm			0.25ml (CEL)	Boutwell and Bosch 1958	coal
CHRONIC EXPOSURE								
Cancer								
5	Mouse	70 wk 2x/wk	Derm			1 drop (CEL) undiluted	Lijinsky et al. 1957	coal
6	Mouse	Life 3x/wk	Derm			20% (CEL)	Poel and Kammer 1957	coal

d = day(s); wk = week(s); x/d = times per day; x/wk = times per week; Derm = dermal; Resp = respiratory; CEL = cancer effect level; ml = milliliters; > = greater than.

dermal exposure. Creosote burns were observed in construction workers who handled wood treated with creosote (presumably coal-tar creosote) (Jonas 1943). Exposure levels were not specified. It was found that 70% of the burn cases were mild and were characterized by erythema of the face. These symptoms were more marked on the cheeks, nose, forehead, and posterior part of the neck. The remainder of the burn cases (30%) were more severe and were characterized by intense burning, itching, and considerable subsequent pigmentation followed by desquamation. There is no way to determine, given the information provided, whether this response was due to primary irritation or an allergenic response. Conjunctivitis was seen in 15% of the men, with 3% of these showing corneal injuries. Exposure to the sun exacerbated these effects. The skin injuries were reversed with thorough washing, application of Foille solution (which contains various calcium salts, benzocaine, sulphur and vegetable oil base), and cessation of exposure.

Other studies confirm that coal-tar creosote is capable of inducing phototoxicity of the skin. Phototoxicity is an exaggerated response to sun exposure characterized by excessive sunburn. The usual sunburn is produced by UVB light, whereas a phototoxic skin response occurs following exposure to UVA light (Baker and Fannick 1981). Coal-tar creosote exposure was evaluated in six dock builders, all male of Scandinavian descent with fair features and an average of 16.6 years spent as pile-drivers (Baker and Fannick 1981). It was found that the dermal and ocular burning and irritation experienced by these workers upon dermal contact with wood treated with coal-tar creosote was exacerbated on hot or sunny days. Skin examinations of these dermally exposed workers revealed erythema and dry peeling skin on the face and neck with irritation and folliculitis on the forearms. These symptoms were worse on hot or sunny days, at which time red, swollen, and puffy eyes were observed. Thus, phototoxicity compounds the irritative response of the skin to coal-tar creosote. No skin tumors were observed. Exposure levels of coal-tar pitch volatiles measured were considered to represent the minimum ambient air exposure in the barge area because of unusual environmental sampling conditions. These levels ranged from below the detectable limit to 0.06 mg/m^3 for breathing zone samples and from below the detectable limit to 0.02 mg/m^3 for area samples.

Coal-tar creosote has been reported to produce other types of noncancerous skin lesions as well as burns and irritation following dermal exposure. Haldin-Davis (1935) described the case of a man employed in the activity of dipping wood in creosote tanks who received "heavy" dermal exposure to creosote (level not determined) on the face, trunk, and thighs. He subsequently developed a number of lesions on the hands, forearms, and thighs. One of these lesions was excised and examined and classified as a (benign) squamous cell papilloma.

The National Institute for Occupational Safety and Health (NIOSH) was called in to investigate potential employee-related health effects in mixers and laborers exposed to coal-tar products in a factory (Chrostek 1980). Six of seven environmental samples collected exceeded the NIOSH Permissible Exposure Limit (PEL) for coal-tar products (cyclohexane solubles, which includes creosote) of 0.1 mg/m^3. Exposures were reported to be as high as 1.42 mg/m^3. Because environmental levels significantly exceeded the PEL, it is likely that considerable inhalation exposure occurred. One worker reported the need for medical treatment when creosote splashed in his eye, and another claimed that he was hospitalized for 3 days after experiencing convulsions following an incident where he was splashed with creosote. The medical records for these two men were not reviewed.

Skin irritation is also observed in laboratory animals following dermal exposure to creosote. Rabbits given single dermal applications of undiluted coal-tar creosote exhibited slight to moderate erythema and moderate edema followed by severe hyperkeratosis (Pfitzer and Gross 1964). These same investigators also found that instillation of 0.1 mL undiluted coal-tar creosote in the eyes of rabbits produced a redness of the conjunctiva with congested vessels that resolved within seven days (Pfitzer and Gross 1964). The effects of dermally applied coal-tar fractions, derived from creosote and anthracene oils by high-temperature boiling, were studied in mouse tail skin at concentrations of 5% and 10% (acids) in paraffin by Wrench and Britten (1975). Several of the fractions caused irritation, and some caused peeling and epidermal thickening. The authors concluded that the acids that boiled in the range from 280° to 340°C have a more specific action in inducing granular layers than the parent tars, oils, or whole acids at similar concentrations. This study is of limited value because the chemical composition of the acid fractions was not defined, and no dose levels could be quantified. It can only be concluded that certain fractions of coal-tar creosote irritate mouse skin.

Creosote also irritates other types of tissue. The effects of beechwood creosote (dose not specified) on the periapical tissue (the connective tissue surrounding the apex of the tooth) were studied in 10 teeth from 4 different dogs 7 days after its application following root canal surgery (Attalla 1968). Beechwood creosote application resulted in localized inflammatory changes and occasional abscess formation in the periapical region, presumably due to tissue damage caused by coagulation of proteins. Bone resorption was also observed in the alveolar process. The authors concluded that the beneficial disinfectant properties of creosote may be outweighed by its irritant effect following root canal surgery.

In summary, dermal application of either coal-tar or beechwood creosote results in mild-to-severe irritation of the skin, connective tissue, and eyes, as well as benign skin lesions in both humans and animals. Coal-tar creosote also induces phototoxicity, so exposure to the sun exacerbates its irritant effects. This has important implications for individuals living in areas surrounding hazardous waste sites who may come in contact with creosote-contaminated soils.

2.2.3.3 Immunological Effects

Several cases of acute allergic dermatitis have been reported following contact with creosote bush resin. Smith (1937) described the case of a patient who presented with erythematous and vesicular dermatitis of the face, the upper part of the neck, and the backs of the hands after collecting creosote bush. Patch tests confirmed the existence of an allergy to this plant. Leonforte (1986) reported six cases of acute allergic dermatitis subsequent to contact with a creosote bush and confirmed by a patch test. Two cases were a result of "casual occupations," two were a result of household remedies, and two were a result of burning the bush. Based on his findings, the author concluded that the allergens are probably contained in the plant's perfume, are volatile, and are not destroyed by heat. The relevance of these findings to individuals who live in areas surrounding hazardous waste sites and who will most likely be exposed to coal-tar creosote is questionable. Creosote bush resin differs from creosote extracted from coal and wood tar, but all contain phenolic derivatives. It is not known whether these derivatives are the allergens in creosote bush resin.

2.2.3.4 Neurological Effects

A worker who was splashed with creosote in a refinery claimed that he was hospitalized for 3 days after experiencing convulsions (Chrostek 1980). The medical records for this man were not reviewed, so it cannot be concluded that creosote exposure was responsible for his convulsions.

No studies were located regarding neurologic effects in animals following dermal exposure to creosote.

2.2.3.5 Developmental Effects

No studies were located in the literature regarding developmental effects in humans following dermal exposure to creosote.

The only available study in animals reported that dermal contact with creosote-treated wood produced fetotoxic effects in pregnant sows (Schipper 1961). Four sows were confined to wooden farrowing crates for 2-10 days before delivery. The platforms of the crates were coated with 3 brush applications of a commercial wood preservative containing 98.5% coal-tar creosote. Following this gestational exposure to creosote, 24 of the 41 pigs delivered were dead at birth, and 11 pigs died by day 3 post-farrowing. The surviving pigs had rough skin and suffered from dehydration and severe diarrhea. The pigs failed to gain weight until they were 5-6 weeks old. No toxic effects on the sows were reported. On the contrary, four sows confined to untreated lumber crates at least 24 hours before farrowing delivered 36 pigs; 1 died within 24 hours and 3 died post-farrowing. No toxic effects were noted in mothers or baby pigs. The study limitations include unequal duration of exposure between treated and untreated groups, and the lack of statistical analysis of the reported results. Moreover, although creosote was absorbed in sufficient quantities via dermal contact by pregnant sows, the actual dose producing toxic effects in pigs cannot be determined. Therefore, neither dose-response nor NOAEL and LOAEL values for the developmental toxicity of creosote for pigs can be determined.

2.2.3.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following dermal exposure to creosote.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following dermal exposure to creosote. The mutagenic activity of urine samples taken from workers briefly exposed to coal-tar creosote vapors in a wood preserving factory was investigated (Bos et al. 1984a, see Section 2.2.1.7, "Inhalation Exposure, Genotoxic Effects"). However, the possibility of dermal exposure by contact with residual surface creosote cannot be excluded in this study. The urine samples were negative for mutagenic activity following exposure at work. The data are not sufficient to draw a conclusion regarding the genotoxic potential of dermal contact with creosote vapors in humans, but they do suggest that extrapolation of mutagenicity tests on a single component (i.e., PAHs) may not predict the action of the mixture.

2.2.3.8 Cancer

Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote exposure with the development of skin cancer (Cookson 1924; Henry 1947; Lenson 1956; MacKenzie 1898; O'Donovan 1920). These papers reported a similar disease etiology for different groups of workers exposed to creosote that included the development of dermatoses, such as squamous papillomas, that progressed to carcinoma, usually squamous-cell carcinoma. The latency period for the development of dermatoses, such as squamous papillomas, was usually 20-25 years (Cookson 1924; Henry 1946, 1947; O'Donovan 1920). The latency period for the development of carcinoma averaged 25 to 30 years (Cookson 1924; Henry 1946, 1947; O'Donovan 1920). Worker exposure in the past was much greater than it now is because of less-sophisticated industrial practices used in the past, the lack of knowledge concerning occupational hygiene, and the current recognition of the dangers of excessive exposure to the health of workers. Other factors that should be considered when extrapolating the findings of this older literature to present conditions are the role of exposure to ultraviolet radiation in the form of sunshine in these workers (ultraviolet radiation is now known to be a major cause of skin cancer), the composition of the creosote products, and other health factors that differ in Great Britain prior to 1940 and the present. Although these studies lack information concerning specific exposures and did not consider other risk factors for the development of skin cancer, when taken as a group, they present convincing evidence of a relationship between chronic creosote exposure, phototoxicity, and the development of skin carcinoma in humans.

Creosote exposure has also been associated with multiple myeloma in a case/referent study of a Swedish population (Flodin et al. 1987, see Section 2.2.1.8). This relationship needs to be investigated further by more sophisticated studies.

On the other hand, several studies are available that suggest that there is no association between exposure to creosote or other coal-tar products and cancer in humans. No increased incidence of non-melanoma skin cancer was observed in 426 patients 25 years after they had undergone 4 years of coal-tar medicinal therapy in combination with ultraviolet light for the treatment of atopic dermatitis and neurodermatitis (Maugham et al. 1980). This study is limited in that follow-up occurred in only 72% of the patients, and there was no discussion of recall bias or of the effects of mobility (i.e., relocation of the study participants) on the results. In a 25-year retrospective study of 280 psoriatic patients treated with crude coal-tar in combination with ultraviolet radiation at the Mayo clinic, it was found that the incidence of skin cancer in these patients was not significantly increased above the expected incidence for the general population (Pittelkow et al. 1981). However, it should be noted that in investigations on populations using therapeutic coal-tar skin products, exposure was to a different coal tar mixture. Creosote is a lower boiling distillate fraction of crude coal-tar than the components contained in the skin products, and creosote does not contain the concentrations of putative carcinogenic PAH compounds that are present in the coal-tars contained in the skin products.

Another study was located that reported that there was no increase in the risk of skin, bladder, or lung cancer in wood treatment plant workers (Tabershaw Occupational Medicine Associates 1980). Limitations in this study include: the study population was small; the study population was comprised of 46.5% blacks who experience a very low incidence of skin cancer as compared to whites, thus biasing the results; the exposure and follow-up periods did not allow a long enough latency period for tumor development; and there was no verification provided that those studied were actually exposed to creosote or coal-tar.

A large body of evidence exists that coal-tar creosote is carcinogenic when applied to the skin of laboratory animals. Many of the early studies are limited in that they lack appropriate negative control data, the dose of creosote and the chemical composition of the fractions studied were not quantified, and no other tissues were generally examined. The results from later studies that include appropriate control groups are consistent with the earlier studies that found that creosote is carcinogenic following dermal application to rodent skin. Six representative dermal carcinogenicity studies are reviewed below, and the relevant cancer effect levels are presented in Table 2-2.

The tumor-promoting potential of creosote was evaluated by applying various fractions (e.g., basic, phenolic, and neutral) to the skin of mice in conjunction with benzo(a)pyrene (B[a]P) (Cabot et al. 1940). The various fractions of creosote oil were prepared by distillation and separation. Ninety percent of the creosote oil distilled between 160° and 300°C. The basic fraction was removed with aqueous hydrochloric acid. The phenolic fraction was removed with aqueous sodium hydroxide. The remaining neutral fraction was then steam distilled. The composition of the various fractions was not specified. Four of the test solutions antagonized the tumorigenic effects of B[a]P, but in three instances this antagonistic effect was considered to be secondary to skin damage. Only the phenolic fraction seemed to exhibit a primary antagonistic effect. Three fractions (basic, neutral, and neutral distillate) exhibited apparent promoting effects.

The potential of basic fractions of creosote to accelerate tumor induction by known carcinogens was evaluated by Sall and Shear (1940). A 1% solution of the basic fraction of creosote oil in benzene was dermally applied to female strain A mice alone or in conjunction with 0.05% or 0.02% B[a]P. The basic fraction alone did not induce skin tumors, but when applied in conjunction with either concentration of B[a]P, skin tumors appeared more rapidly than when B[a]P alone was applied. Maximum tumor induction was seen between 28 and 42 weeks; 19 or 20 mice developed tumors. The composition of the basic fraction was not specified, but it is reported to be noncarcinogenic.

The ability of creosote to induce lung tumors after dermal application to mice was studied when it was observed that mice housed in creosote-treated wooden cages had a high incidence of lung tumors (Roe et al. 1958). Dermally applied creosote (0.25 mL undiluted twice weekly for 8 months) induced 5.8 lung adenomas/mouse in mice that were reared in stainless steel cages. Creosote treatment following the same regimen in mice reared in creosote-treated cages induced 10.8 lung adenomas/mouse. Untreated controls reared in untreated cages exhibited 0.5 lung adenomas/mouse. A high incidence of skin tumors was also observed in the creosote-treated mice reared in either type of cage. In a second experiment, topical application of "one drop" of creosote twice a week for only 4 weeks induced lung adenomas but not skin tumors in mice reared in stainless steel cages. This study demonstrated that creosote induces tumors in the lungs and skin of mice when dermally applied. Rearing animals in creosote-treated wooden cages exacerbated the tumorigenic effect of dermally applied creosote. Based on this study, lung tumors may be a more sensitive end point of creosote tumorigenic activity than skin tumors.

Seven groups of thirty female albino mice each were treated with dimethylbenzanthracene (DMBA) and creosote (0.25 mL of undiluted creosote oil), alone and combinations of the two to evaluate the carcinogenic, initiating, and promoting activity of creosote on mouse skin (Boutwell and Bosch 1958). Creosote alone, DMBA and creosote, and creosote with croton oil all induced the development of papillomas and carcinomas. Tumors first appeared at 10-20 weeks of application. DMBA pretreatment shortened the latent period and increased the tumor yield of creosote treatment, but since almost a nearly maximal tumor induction response (i.e., percent of mice with papillomas was just below 100) was seen with creosote alone, tumor-promoting activity of creosote could not be definitely proven. The initiating activity of creosote was demonstrated by its ability to induce tumors when applied prior to croton oil treatment (croton oil alone was without effect). Creosote alone or in combination with DMBA or croton oil induced papilloma formation more slowly, and carcinomas appeared by 14 weeks and accumulated more rapidly than in the DMBA plus croton oil group. Thus, this study demonstrated the carcinogenic and tumor-initiating activity of creosote on mouse skin.

The complete carcinogenic and tumor-promoting activity of undiluted creosote, a 10% solution of creosote oil, and 2% solution of the basic fraction of creosote was studied when dermally applied to mice (Lijinsky et al. 1957). Undiluted creosote alone induced 23 skin tumors (16 malignant) in 13 of 26 treated mice with a latent period of 50 weeks. The authors concluded that creosote alone has a carcinogenic activity comparable to a 0.01% solution of dimethylbenzanthracene (DMBA). When applied as a promoter following a single application of DMBA, 32 skin tumors (26 malignant) were observed in 17 of 30 mice with a latent period of 39 weeks. The basic fraction did not act as a tumor promoter when administered after a single application of DMBA. Thus, creosote appeared to enhance the carcinogenic activity of DMBA, but the promoting effect was not strong, when the results were compared to DMBA positive controls.

The carcinogenic activity of two high-temperature-derived creosote oils ("light" and "blended") was studied by Poel and Kammer (1957). The principal components of light oil are benzene, toluene, xylene and solvent naphtha. Blended oil is a mixture of creosote oil, anthracene oil and the oil drained from the naphthalene recovery operation. Its principal components are methylated naphthalenes, acenaphthene, fluorene, phenanthrene, anthracene and carbazole. The oils were applied by drops to the skin of mice at concentrations of 20%, 50%, or 80% three times a week for life. Both oils induced skin tumors in every exposed mouse by 21 to 26 weeks of application. Several mice exhibited metastases to the lungs or regional lymph nodes. The fractions tested did not contain B[a]P, so the authors concluded that the carcinogenic activity of creosote was not due to B[a]P.

In conclusion, the results of these studies indicate that coal-tar creosote and several of its fractions are carcinogenic when applied to the skin of mice. Dermally applied creosote can also act as a tumor-initiating agent when applied prior to croton oil treatment and can enhance and accelerate tumor induction by B[a]P. Thus, it is likely that individuals whose skin comes into contact chronically with creosote would be at higher risk for cancer, particularly when exposure to other carcinogenic substances also occurs, as is a likely scenario in areas surrounding hazardous waste sites.

2.3 TOXICOKINETICS

Specific information regarding the toxicokinetics of creosote is limited. Several compounds have been detected in creosote, yet there are no definitive data on which of these compounds people are exposed to in wood-treatment plants or at hazardous waste sites. Analyses have revealed that PAHs are the major components of the creosote mixture (EPA 1981a). Hence, pharmacokinetic studies on PAHs can be used as surrogates for creosote. However, this is only speculative given the possible toxicokinetic interactions that occur among the PAHs and other components in the creosote mixture, and will be used only when data on creosote are not available. For more information on the toxicokinetics of PAHs, please refer to the ATSDR Toxicological Profile for Polycyclic Aromatic Hydrocarbons (ATSDR 1990).

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located in humans or animals regarding the direct analysis of the extent or rate of creosote absorption following inhalation exposure. However, there is evidence to suggest that inhalation absorption occurs. Employees of a creosote-impregnating plant excreted 1-hydroxypyrene, a metabolite of the creosote component, pyrene, in their urine (Jongeneelen et al. 1985). The presence of this metabolite in the urine suggested that creosote components were absorbed and metabolized following inhalation exposure. However, it is also possible that some dermal exposure may have occurred as well.

PAHs extracted from coal fly ash were intratracheally administered to pregnant rats at a dose of 20 mg/kg. The presence of the PAHs in the maternal and fetal lungs and livers indicated that pulmonary absorption occurred (Srivastava et al. 1986).

2.3.1.2 Oral Exposure

No studies were located in humans and animals regarding the direct analysis of the extent or rate of creosote absorption following oral exposure. However, the presence of creosote metabolites in the urine of humans and rabbits receiving calcium creosotate (a calcium salt of creosote) tablets was evidence that creosote was absorbed following ingestion (Fellows 1937, 1939b). Furthermore, evidence exists that certain PAHs found in creosote such as anthracene (Rahman et al. 1986), benzo(a)pyrene (Hecht et al. 1979; Rahman et al. 1986; Rees et al. 1971; Yamazaki et al. 1987), chrysene (Chang 1943;

Modica et al. 1983), and phenanthrene (Rahman et al. 1986) are absorbed following oral administration in animals.

2.3.1.3 Dermal Exposure

No studies were located in humans and animals regarding the direct analysis of the extent or rate of creosote absorption following dermal exposure. However, reports of workers who developed cancer subsequent to dermal exposure suggested that creosote was absorbed through the skin (Cookson 1924; Henry 1946, 1947; Lenson 1956). It can also be concluded that dermal absorption occurred as evidenced by the development of skin tumors (Boutwell and Bosch 1958; Lijinsky et al. 1957; Poel and Kammer 1957; Roe et al. 1958) and lung tumors (Roe et al. 1958) in mice following the dermal application of creosote. Based on these occupational exposures and animal toxicity studies, it would appear that dermal absorption of creosote occurs.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located in humans or animals regarding the distribution of the creosote mixture following inhalation exposure. However, an occupational study indicated that creosote is absorbed and metabolized as evidenced by the appearance of 1-hydroxypyrene (a metabolite of pyrene, a component of creosote) following inhalation exposure (Jongeneelen et al. 1985). Because creosote is composed of hydrocarbons, creosote is likely to distribute to lipid-rich tissues. Creosote is also likely to distribute to the liver as evidenced by the presence of metabolites in the urine.

When [^{3}H]-benzo[a]pyrene was administered intratracheally to rats at a dose of 0.001 mg/kg, radioactivity was distributed to all tissues. During the 6 hours following administration, more than 20% of the dose was detected in the carcass. The activity steadily increased in the intestine and the intestinal contents over the 6 hours. Levels of activity in the liver and lung were moderate and declined over time. Trace amounts of activity were detected in other tissues (Weyand and Bevan 1987).

Intratracheal administration of [^{3}H]-benzo[a]pyrene along with the benzene extract of coal fly ash to pregnant rats (20 mg/kg/day) on days 18 and 19 of gestation resulted in their distribution to the maternal lung and liver. The amount of radioactivity found in the maternal liver was approximately 68% of the amount of radioactivity found in the maternal lung. The amount of radioactivity found in the placenta, fetal lung, and fetal liver was approximately 4%, 1.9%, and 1.4%, respectively, of the amount of radioactivity found in the maternal lung (Srivastava et al. 1986). Much of the radioactivity was attributable to metabolites. These results suggest that components of creosote and their metabolites can pass through the placenta and distribute to fetal tissue.

2.3.2.2 Oral Exposure

No studies were located in humans or animals regarding the distribution of creosote following ingestion. Based on chemical structure, it is likely that PAHs would have a strong affinity for adipose tissue. Benz[a]anthracene, chrysene, and triphenylene distributed to all tissues following oral administration (22.8 mg/kg) to female rats, but its greatest distribution was to adipose tissue. In this study, benz[a]anthracene concentrations in adipose were 10 times higher than in other tissues (Bartosek et al. 1984).

The distribution of nonmetabolized PAHs is dependent on their water-solubility. The more water-soluble PAHs, like triphenylene, are generally more available to tissues other than fat (Bartosek et al. 1984). In humans, distribution of creosote following ingestion is likely to be qualitatively similar to that seen in the animal studies. The lipophilicity of PAHs allows the chemicals to be readily absorbed and preferentially accumulated in fatty tissues. Furthermore, PAHs are likely to be present in adipose and highly perfused organs such as the lungs and liver.

2.3.2.3 Dermal Exposure

No studies were located in humans or animals regarding the distribution of creosote following dermal exposure. Distribution of creosote in humans following dermal exposure is expected to be qualitatively similar to that seen in animals or in humans following any route of exposure.

2.3.3 Metabolism

Generally, the PAH components of creosote are metabolized by oxidative enzymes to generate active metabolites that can bind to macromolecules. The metabolic profiles vary among species and compounds, but the components follow the same reaction pathways. Hence, the metabolites are structurally very similar. The proposed metabolic scheme for a representative PAH, benzo(a)pyrene is presented in Figure 2-2. The principal products include phenols, dihydrodiols, quinones, anhydrides and conjugates of these products (Autrup and Seremet 1986; Dahl et al. 1985; Geddie et al. 1987; Hopkins et al. 1962; Jongeneelen et al. 1985; Petridou-Fischer et al. 1988; Povey et al. 1987; Rice et al. 1986; Weyand and Bevan 1987).

2.3.3.1 Inhalation Exposure

Workers in a creosote-impregnating plant were exposed to creosote by inhalation. The creosote that these employees inhaled contained 19.8 mg pyrene/g creosote (approximately 2%). A metabolite of pyrene, 1-hydroxypyrene, was detected in their urine at levels that were above the mean values of controls (Jongeneelen et al. 1985). The identification of PAH metabolites in the urine could serve as a method of biological monitoring of

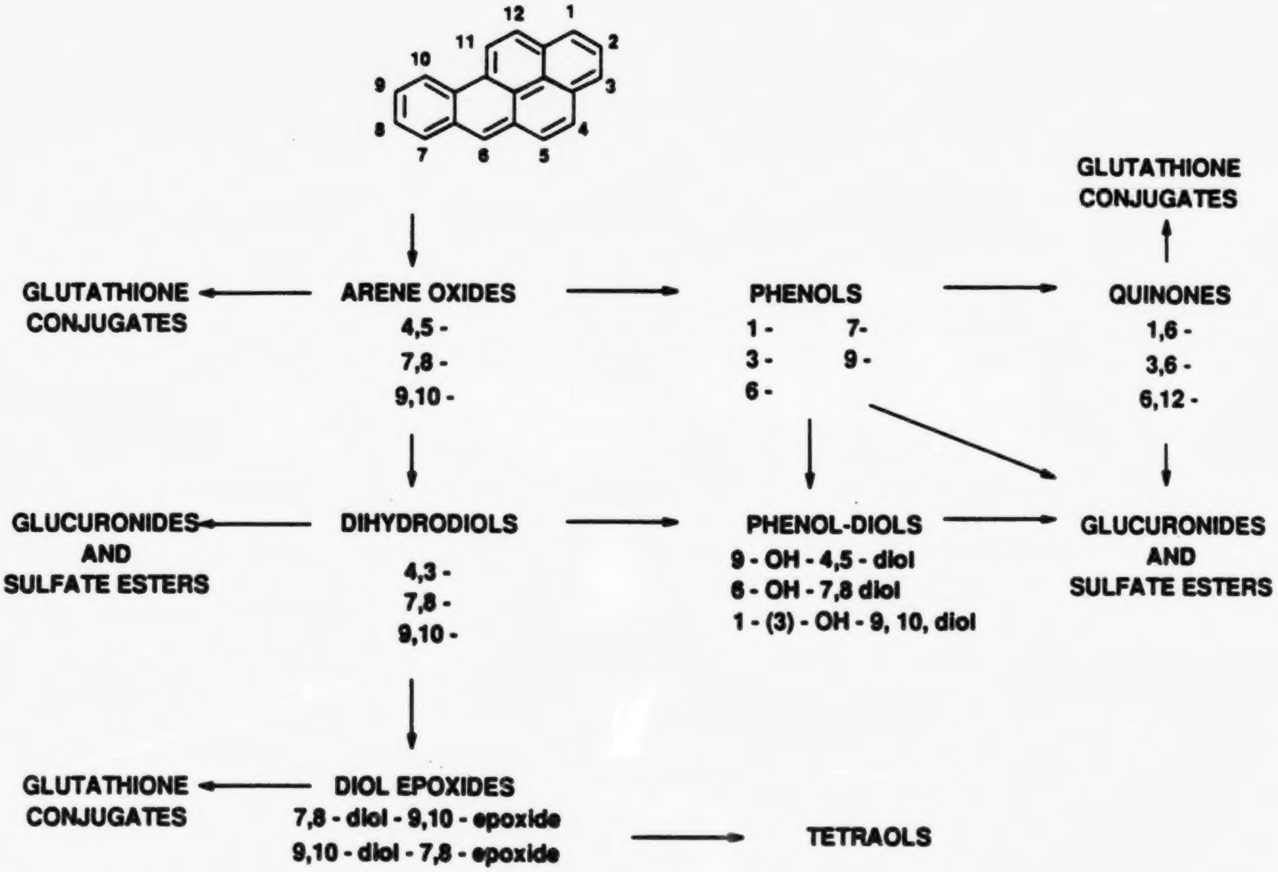
12
1
2
11
10
9
3
8
4
7
6
5
GLUTATHIONE CONJUGATES
GLUTATHIONE CONJUGATES
ARENE OXIDES
4,5 -
7,8 -
9,10 -
PHENOLS
1 -
3 -
6 -
7-
9 -
QUINONES
1,6 -
3,6 -
6,12 -
GLUCURONIDES AND SULFATE ESTERS
DIHYDRODIOLS
4,3 -
7,8 -
9,10 -
PHENOL-DIOLS
9 - OH - 4,5 - diol
6 - OH - 7,8 diol
1 - (3) - OH - 9, 10, diol
GLUCURONIDES AND SULFATE ESTERS
GLUTATHIONE CONJUGATES
DIOL EPOXIDES
7,8 - diol - 9,10 - epoxide
9,10 - diol - 7,8 - epoxide
TETRAOLS

FIGURE 2-2. Proposed Metabolic Scheme for Benzo(a)pyrene

exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where creosote has been detected.

2.3.3.2 Oral Exposure

Calcium creosotate was orally administered to humans at daily doses of 7-30 mg/kg for 3 days. Calcium creosotate phenols were excreted in the urine. Also, large unspecified doses of calcium creosotate were orally administered to rabbits. Analysis of the rabbit urine revealed that free and conjugated phenols were excreted (Fellows 1939b).

Rats receiving a single dose of either 0.0002, 0.002, 0.02, 0.2, or 2.0 mg pyrene/kg by gavage in olive oil excreted 1-hydroxypyrene in the urine in a dose-dependent manner. This metabolite could be detected up 96 hours after administration. No pyrene was excreted (Jongeneelen et al. 1985).

It is evident in both human and animal studies that hydroxylation is a principal oxidative pathway of PAH metabolism, and consequently, creosote metabolism. In these studies, there were no discussions to suggest that the researchers attempted to identify other metabolites.

2.3.3.3 Dermal Exposure

Two patients suffering from eczema on the arms and legs were treated for several days with an ointment containing 10% pix lithanthracis dermata (coal-tar). The daily dermal dose was approximately 1 mg/kg. Analysis of the urine samples collected from these patients prior to treatment and in the morning and evening of the first three days of treatment showed that 1-hydroxypyrene (a metabolite of pyrene which is a PAH component of coal-tar) was excreted at levels 200 times that which was detected before the treatment started (Jongeneelen et al. 1985). Thus, based on these results, it appears that PAH components of coal-tar creosote are metabolized following dermal exposure in humans.

2.3.4 Excretion

Excretion of the PAH compounds of creosote is controlled by their rate of metabolism. Excretion of these metabolites or any remaining parent compound is primarily in the bile and the feces. Weyand and Bevan (1987) demonstrated this by cannulating the bile ducts of rats that received [^{3}H]-benzo[a]pyrene intratracheally. Those rats with the biliary cannulas had significantly lower levels of activity in their intestines, intestinal contents and stomach than rats without biliary cannulas. Sanders et al. (1986) showed that PAHs were primarily removed in the feces after dermal administration of [^{14}C]-benzo[a]pyrene and [^{14}C]-7,12-dimethylbenz[a]-anthracene, suggesting hepatobiliary excretion. Urinary excretion also occurs, but to a lesser extent than the other routes.

2.3.4.1 Inhalation Exposure

No studies were located in humans or animals regarding the excretion of creosote following inhalation exposure.

2.3.4.2 Oral Exposure

No studies were located in humans or animals regarding the excretion of creosote following oral exposure.

2.3.4.3 Dermal Exposure

No studies were located in humans or animals regarding the excretion of creosote following dermal exposure.

2.4 RELEVANCE TO PUBLIC HEALTH

Creosote is a complex mixture of organic substances. It can be derived by distillation from coal (coal-tar creosote) or wood (beechwood creosote). Another form is a resin from the leaves of the creosote bush. The chemical composition of creosote varies considerably depending on the source of the coal, wood, or plant and the design and attendant operating conditions (temperature, gas distillation systems, etc.) used to produce the creosote. Coal-tar creosote is reported to contain over 300 compounds (EPA 1978), the major components of which are PAHs, tar acids (phenol, cresols and xylenols), and tar bases (pyridine and lutidine derivatives). Coal-tar creosote is used primarily as a wood preservative. Beechwood creosote consists mainly of phenol, cresol, guaiacol, xylenol and creosol. It has been used therapeutically as an expectorant and a disinfectant. Creosote bush resin consists of phenolics (which account for 83-91% of the total resin), neutrals (e.g., waxes), basics (e.g., alkaloids), and acidics (e.g., phenolic acids). Given the current widespread use of coal-tar creosote as a wood preservative and its past pesticidal applications, it is the form of creosote most likely to be present at hazardous waste sites.

There is relatively little information available regarding the systemic effects of ingested creosote. However, oral exposure via ingestion of contaminated drinking water is most likely not a highly significant route of exposure to creosote at hazardous waste sites, given its low solubility in water. Most of the available recent information on the adverse effects of ingested creosote in both humans and animals is on beechwood creosote. These studies indicate that the liver, kidney, central nervous system, and cardiovascular system may be adversely affected by beechwood creosote following primarily acute exposure, although the mechanism of action for these effects is not known. The relevance of these findings in animals with exposure to beechwood creosote to humans exposed to coal-tar creosote is not known. Although the two forms of creosote contain some components in common (e.g., phenolic derivatives) it is not known whether the toxic effects observed after exposure to beechwood creosote can be attributed to the phenol components and thus, extrapolated to coal-tar creosote. Coal-tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues that it comes in contact with, such as the skin and eyes. Acute ingestion of coal-tar creosote appears to affect primarily the kidney and liver. The mechanism of action for coal-tar creosote-induced toxicity is not defined, but is most likely due to the activity of the PAH components.

Much of the information available on the health effects of coal-tar creosote must be inferred from experimental animal and in vitro data on the components of the creosote mixture (i.e., PAHs). Extrapolation of these results to possible human health effects following exposure to creosote must consider the possible interactions of the mixture, such as co-carcinogenicity, co-mutagenicity, additivity, promotion, and antagonism. The extent to which these interactions modify the expression of creosote toxicity in humans is not known.

Death. No information was available on the lethal effects of creosote following inhalation or dermal exposure in humans. No deaths were observed in rats exposed to near saturated vapors of coal-tar creosote for one hour (concentration estimated to be less than 0.033 mL/L) (Pfitzer and Gross 1964). The exposed animals showed signs of slight eye and nose irritation and slight dyspnea. All rats exhibited weight gains comparable to the control animals and there were no treatment-related lesions observed at necropsy. The dermal LD_{50} in rabbits has been estimated to be greater than 7.95 g/kg (Pfitzer and Gross 1964).

Ingestion of creosote can be fatal to both humans and animals. In the case reported by Bowman et al. (1984), death following ingestion of creosote (form and quantity not specified) was attributed to multi-organ failure. Death has been reported to occur in adults and children 14 to 36 hours after the ingestion of about 7 g or 1-2 g creosote, respectively (Clayton and Clayton 1981). The latter anecdotal information is of limited value because it was obtained from a secondary source that provided no supporting documentation. The oral LD_{50} for coal-tar creosote is reported to be 433 mg/kg in the mouse and 725 mg/kg in the rat (RTECS 1988). However, another study reported an acute oral LD_{50} of 1700 mg/kg in the rat (Pfitzer and Gross 1964). The reasons for this discrepancy in LD_{50} values are not known. Based on these data, coal-tar creosote can be classified as mildly to moderately toxic. Beechwood creosote is lethal to animals, although the doses required to produce death are relatively high (300-525 mg/kg). Death is preceded by signs of central nervous system intoxication following acute exposure in both humans and animals. Given the relatively high oral doses required to cause death following acute exposure in both humans and animals, individuals living in areas surrounding hazardous waste sites contaminated with creosote may not be at high risk for death due to acute ingestion of creosote.

Systemic Effects. A slightly higher incidence of bronchitis or thickening of the tracheal mucous membrane was observed in mice fed beechwood creosote for 52 weeks. This effect was considered secondary to irritation resulting from long-term inhalation exposure to volatile (but unidentified) components of creosote in the feed. No toxic respiratory effects have been reported following coal-tar creosote exposure in either humans or animals. The airborne component chemicals in coal-tar creosote have not been well defined. However, based on the results discussed above, it can be assumed that some components of beechwood creosote, that may be common to coal-tar creosote are irritating to the respiratory tract.

A report was found in the older literature that described the case of a woman who experienced hypertension attributed to creosote exposure by "self-medication" for chronic bronchitis (Robinson 1938). Cardiovascular collapse has also been reported to occur following the ingestion of lethal doses of coal-tar creosote in humans (Clayton and Clayton 1981). These cases are anecdotal and occur in isolated instances. There is often a lack of exposure data, and the possibility of confounding factors limit the usefulness of these findings. Furthermore, adverse creosote-induced cardiovascular effects have not been reported in animals. Thus, it is not likely that the cardiovascular system is a major target organ of toxicity from creosote exposure.

Ulceration of the oropharynx and petechial hemorrhages over the gastrointestinal serosal surfaces were noted at autopsy in the case of a 70-year-old man who died following the ingestion of "industrial" creosote (Bowman et al. 1984). This acute tissue damage was attributed to a corrosive action of phenol (a component of creosote) via its ability to denature and precipitate proteins. Animals that died following the administration of single gavage doses of coal-tar creosote in an acute range-finding study (doses ranged from 2.52-5.00 mg/kg) exhibited hyperemia and distention of the stomach upon necropsy. Similarly, rabbits that died following single dermal applications of undiluted coal-tar creosote exhibited hyperemia of the intestines (Pfitzer and Gross 1964). The toxicological significance of these changes is not known. Thus, given that gastrointestinal lesions were observed in only one isolated instance in humans, and the fact that only mild creosote-induced gastrointestinal effects of unknown toxicological significance have been reported in animals, it is likely that the gastrointestinal system is a target organ of toxicity only after the ingestion of relatively high doses of creosote.

Various hematological and clinical chemistry parameters have been observed to be altered by dietary exposure to beechwood creosote in rats and mice (Miyazato et al. 1981, 1984a,b). The only effect considered to be treatment-related by the authors was an increase in serum cholesterol in both rats and mice. The toxicological significance of this change is not known, particularly with regard to individuals exposed to coal-tar creosote in areas surrounding hazardous waste sites. No adverse hematological effects have been reported in humans exposed to creosote.

Degeneration and necrosis of hepatocytes were observed at autopsy in the case reported by Bowman et al. (1984). Given the advanced age of this man, the possibility of confounding factors, and the lack of comparison data, it is not possible to definitively attribute these effects to creosote ingestion. Dietary exposure to beechwood creosote induces changes suggestive of liver injury in rats and mice (increase relative liver weights and increased liver enzymes). However, no treatment-related changes were observed at histological evaluation (Miyazato et al. 1981, 1984a,b), and the toxicological significance of these changes with regard to individuals exposed to coal-tar creosote in areas surrounding hazardous waste sites is not known.

Observations made in both humans and animals suggest that creosote has the potential to induce adverse effects in the kidney. Prior to death, the patient described by Bowman et al. (1984) became acidotic and anuric, indicating kidney failure. Acute renal tubular necrosis was revealed at necropsy. However, the acute tubular necrosis may have been due to vascular insufficiency rather than a direct toxic effect on the kidney. Male rats chronically exposed to beechwood creosote in the diet exhibited an exacerbation of the spontaneously occurring chronic nephrosis normally seen in aging male rats (Miyazato et al. 1984b). Thus, the kidney may be adversely affected by both acute high-level exposure (e.g., following an accidental spill) to coal-tar creosote and chronic low-level exposure to beechwood creosote.

Burns, irritation and benign lesions of the skin (e.g., squamous papillomas), and conjunctivitis of the eyes are the most frequent manifestations of coal-tar creosote toxicity following dermal exposure in both humans and animals. These effects consist of mild-to-severe erythema, intense burning, itching, and subsequent pigmentation followed by desquamation. Involvement of the skin, connective tissue, and eye are often seen. Creosote is also capable of inducing phototoxicity of the skin, so exposure to sun exacerbates its irritant effects. This has important implications for individuals living in areas surrounding hazardous waste sites who may come in contact with creosote-contaminated soils.

Immunological Effects. No adverse immunologic effects have been reported in either humans or animals following exposure to coal-tar or beechwood creosote. Several cases of acute allergic dermatitis have been reported following contact with creosote bush resin. The relevance of these findings to individuals who live in areas surrounding hazardous waste sites and will most likely be exposed to coal-tar creosote is not known. Creosote bush resin differs from creosote extracted from coal and wood tar, but all contain phenolic derivatives. It is not known whether these derivatives are the allergens in creosote bush resin.

Neurological Effects. Adverse neurologic effects have been reported in both humans and animals following the acute ingestion of high doses of coal-tar or beechwood creosote. Such effects include salivation, vomiting, respiratory distress, thready pulse, vertigo, headache, loss of pupillary reflexes, hypothermia, cyanosis, muscle twitching, and convulsions. These observations suggest that creosote may be a general central nervous system stimulant following acute high-level exposure. However, the possibility exists that some of the effects observed in animals that licked treated utility poles may have been due to ingestion of pentachlorophenol. Pentachlorophenol, like creosote, is an oil-borne wood preservative with extensive use in the public utility industry for treatment of utility poles. The neurotoxic effects observed in cattle that licked treated utility poles are more compatible with the metabolic effects (i.e., uncoupling of phosphorylative oxidation) associated with pentachlorophenol (for more information on the effects of pentachlorophenol, please refer to the ATSDR Toxicological Profile for Pentachlorophenol, ATSDR 1989a). Thus, it is not possible to determine conclusively whether creosote is toxic to the central nervous system of animals based on this report. However, no information was found to suggest that chronic low-level exposure to creosote by individuals in areas surrounding hazardous waste sites would result in neurotoxicity.

Developmental and Reproductive Effects. The only available study in animals reported that dermal exposure to creosote-treated wood produced fetotoxic effects in pregnant sows (Schipper 1961). This study was severely limited by lack of exposure data, unequal duration of exposure between treated and untreated groups, and the lack of statistical analysis of the results. No information on adverse developmental or reproductive effects in humans following exposure to coal-tar creosote was found. An increase in relative testis weight was observed in rats administered beechwood creosote in the diet for 3 months (Miyazato et al. 1981). There were no accompanying gross or histopathological lesions of the testes in these animals, so the toxicological significance of this change is not known. Based on these limited data, it is not possible to ascertain the developmental or reproductive risk to humans of exposure to creosote.

Genotoxic Effects. The genotoxic potential of coal-tar creosote has been investigated using exclusively in vitro assays (Bos et al. 1984a,b, 1985, 1987; Mitchell and Tajiri 1978; Simmon and Shepherd 1978). Results of these studies are summarized in Table 2-3. The available genotoxicity data indicate that creosote is an indirect mutagen (i.e., requiring the presence of an exogenous mammalian metabolic system) and induces gene mutation in bacteria and mouse lymphoma cells. The mutagenicity of creosote observed in the conventional S. typhimurium assay is at least partially contributed to by the

TABLE 2-3. Genotoxicity of Creosote In Vitro

End Point	Species (Test System)	Result		Reference
		With Activation	Without Activation	
Prokaryotic organisms:				
Gene mutation	Salmonella typhimurium (histidine auxotrophs)	+	-	Simmon and Shepherd 1978[a]
	S. typhimurium	+ +	- No data	Bos et al. 1985, 1987 Bos et al. 1984b
	S. typhimurium (taped-plate assay; vapor exposure)	+	-	Bos et al. 1985, 1987
	Escherichia coli WP2(TK+/-), (tryptophan auxotroph)	-	-	Simmon and Shepherd 1978[a]
Mammalian cells:				
Gene mutation	Mouse lymphoma cells	+	-	Mitchell and Tajiri 1978
Mammalian body fluids:				
Gene mutation	S. typhimurium (rat urine sample)	+	No data	Bos et al. 1984a
	S. typhimurium (human urine sample; occupational exposure)	-	No data	Bos et al. 1984a

[a] S. typhimurium strains TA1537, TA98 and TA100 showed increases in frameshift mutation; strain TA1535 and E. coli straub WP2 showed no increase in base-pair substitutions. Creosote P1 is a creosote mixture American Wood Preserver's Association (AWPA) specification P-1 product used for foundation piles, freshwater piles, telephone poles, utility poles, fence posts, and other land and fresh-water uses.

+ = positive result; - = negative result

PAHs such as B[a]P and benzanthracene (Bos et al. 1984b). More recently Bos et al. (1987) identified fluoranthene as one of the major volatile components of creosote responsible for the genotoxicity observed in S. typhimurium strains.

In a wood-preserving factory, spot samples collected from the contaminated surfaces including that of creosote-treated wood showed mutagenic activity in S. typhimurium strains TA98 and TA100 (Bos et al. 1984a). Despite the contamination of the work area, no increase in mutagenic activity was detected in the urine samples of workers who inhaled creosote vapors and possibly had skin contact with the residual surface creosote. This negative mutagenic response was probably a result of a low level of creosote exposure or the fact that the components present in the workers' urine were not mutagenic (Bos et al. 1984a). In the same study, mutagenic activity was detected in the urine samples of rats injected intraperitoneally with 25 mg/kg creosote in olive oil.

Coal-tar creosote (type P1[1]) was mutagenic in the mouse lymphoma assay (Mitchell and Tajiri 1978). A dose-related increase in the number of forward mutations was observed in L5178Y mouse lymphoma cells following metabolic activation. Simmon and Shepherd (1978) found that creosote (type P1) produced a mutagenic dose-response and a doubling above background mutation rate in S. typhimurium strains TA1537, TA98 and TA100. S. typhimurium strain TA1535 and Escherichia coli WP2 strain did not demonstrate a positive response with metabolic activation. These results indicate that the genetic mode of action of creosote in S. typhimurium is by frameshift mutation. In recent studies Bos et al. (1984b) examined the mutagenic potential of several fractions of creosote (type P1) in strains TA98 and TA1537. The mutagenicity of creosote was found to be associated at least partially with PAHs (B[a]P and benzanthracene) which were detected in concentrations of 0.18% and 1.1%, respectively (Bos et al. 1983, 1984b). Both compounds, although mutagenic in conventional Ames assay, showed no activity in a S. typhimurium taped-plate assay, probably because of their low volatility (Bos et al. 1985). When creosote samples were further tested for the presence of "volatile mutagens," vapors escaping from creosote increased the number of revertants per plate in the presence of exogenous mammalian metabolic activation system (S9 mix) (Bos et al. 1985). Results of the study suggest that the volatile components of creosote may also contribute to the genotoxic risk from occupational exposure to creosote. In a recent study, Bos et al. (1987) found that creosote contained mutagens which were volatile at 37°C. These were present in the distillation fraction having the highest boiling range (more than 360·C). Upon further high-pressure liquid chromatography (HPLC) and ultraviolet spectroscopic analysis of the fraction and mutagenicity tests, the mutagenic response observed was correlated with the presence of fluoranthene (5.2%) in the creosote samples. The commercially available fluoranthene also tested positive in the taped-plate assay. The available genotoxicity data suggest that creosote has a potential to induce gene mutation in humans exposed via inhalation, and perhaps other routes as well, at hazardous waste sites. However, much of the data discussed above describes the mutagenic activity of selected PAHs. It is not yet known how the various PAHs contained in the coal-tar creosote mixture interact, and what the effects of these possible interactions are on the ultimate genotoxic expression of the mixture.

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[1] Creosote is classified according to a set of standards regarding physical property specifications for creosote that must be met for certain uses of creosote. These specifications are presented in Table 3-4. Type P1/P13 creosote is straight creosote distillate and is used in ground contact, land, and fresh and marine water applications. Type P2 creosote is used by the railroad industry in the treatment of railroad crossties.

Cancer. Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote exposure with the development of skin cancer (Cookson 1924; Henry 1946, 1947; Lenson 1956; O'Donovan 1920). These papers reported a similar disease etiology for different groups of workers exposed to creosote that included the development of dermatoses, such as squamous papillomas, that progressed to carcinoma, usually squamous-cell carcinoma. The latency period for the development of dermatoses, such as squamous papillomas, was usually 20-25 years (Cookson 1924; Henry 1946, 1947; O'Donovan 1920). The latency period for the development of carcinoma was on average 25 to 30 years (Cookson 1924; Henry 1946, 1947; O'Donovan 1920). Worker exposure in the past was much greater than it now is because of less-sophisticated industrial practices used in the past, the lack of knowledge concerning occupational hygiene, and the current recognition of the dangers of excessive exposure to the health of workers. Other factors that should be considered when extrapolating the findings of this older literature to present conditions are the role of exposure to ultraviolet radiation in the form of sunshine in these workers (ultraviolet radiation is now known to be a major cause of skin cancer), the composition of the creosote products, and other health factors that differ in Great Britain prior to 1940 and the present. Although these studies lack information concerning specific exposures and did not consider other risk factors for the development of skin cancer, when taken as a group, and in view of the presence of carcinogenic PAHs, they present convincing evidence of a relationship between chronic creosote exposure and the development of skin carcinoma in humans.

On the other hand, several studies are available that suggest that there is no association between exposure to creosote or other coal-tar products and cancer in humans. No increased incidence of non-melanoma skin cancer was observed in 426 patients 25 years after they had undergone 4 years of coal-tar medicinal therapy in combination with ultraviolet light for the treatment of atopic dermatitis and neurodermatitis (Maugham et al. 1980). This study is limited in that follow-up occurred in only 72% of the patients, and there was no discussion of recall bias or of the effects of mobility (i.e. relocation of the study participants) on the results. In a 25-year retrospective study of 280 psoriatic patients treated with crude coal-tar in combination with ultraviolet radiation at the Mayo clinic, it was found that the incidence of skin cancer in these patients was not significantly increased above the expected incidence for the general population (Pittelkow et al. 1981). In investigations on populations using therapeutic coal-tar skin products, exposure was to a different coal tar mixture. Creosote is a lower boiling distillate fraction of crude coal-tar than the components contained in the skin products, and does not contain the concentrations of putative carcinogenic PAH compounds that are present in the tars (Wright et al. 1985).

Another study was located that reported that there was no increase in the risk of skin, bladder, or lung cancer in wood treatment plant workers (Tabershaw Occupational Medicine Associates 1980). Limitations in this study include: the study population was small; the study population was comprised of 46.5% blacks who experience a very low incidence of skin cancer as compared to whites, thus biasing the results; the exposure and follow-up periods did not allow a long enough latency period for tumor development; and there was no verification provided that those studied were actually exposed to creosote or coal-tar. However, it is possible that because black people are less sensitive to ultraviolet light-induced cancer, their prominence in this study might serve to help isolate the effects of creosote alone from those of ultraviolet light or ultraviolet light plus creosote.

A large body of evidence exists indicating that coal-tar creosote and several of its fractions are carcinogenic when applied to the skin of laboratory animals. Many of the early studies that reported that coal-tar creosote is carcinogenic when dermally applied to rodent skin are limited in that they lack appropriate negative control data, the dose of creosote and the chemical composition of the fractions studied were not quantified, and no other tissues were examined. The results from later studies that include appropriate control groups are consistent with the findings of the earlier studies. Dermally applied creosote can also act as a tumor-initiating agent when applied prior to croton oil treatment, and can enhance and accelerate tumor induction by B[a]P. IARC (1985) has classified creosote as a Group 2A, probable human carcinogen based on limited human evidence and sufficient animal evidence of carcinogenicity. Thus, based on the human and animal data summarized above, it is possible that individuals who chronically come in skin contact with creosote may be at an elevated risk for developing skin cancer, particularly when exposure to other carcinogenic substances occurs, as is a likely scenario in areas surrounding hazardous waste sites.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to creosote are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by creosote are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Creosote

No method is currently available to measure the parent creosote mixture in human tissues or fluids. However, the PAH components of the creosote mixture and their metabolites can be measured in the urine of exposed individuals. For example, Jongeneelen et al. (1985) found a metabolite of creosote, 1-hydroxypyrene, in concentrations of 1-40 μg/g creatinine in urine samples taken from workers who handled approximately 2,400 g creosote/day. The amount of 1-hydroxypyrene detected in urine samples taken during the weekend was less than that detected during the weekdays, when the exposure was presumably higher than on the weekends. No correlation was found between occupational exposure levels and urine levels, so it is not known whether urine metabolites could be detected following exposure to low levels of creosote. The identification of PAH metabolites in the urine could serve as a method of biological monitoring of exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where creosote has been detected following both short- and long-term exposure. However, because of the ubiquitous nature of PAHs in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to creosote. PAH exposure can occur from a variety of sources, and there is no way to determine if creosote was the source.

PAHs form DNA adducts that can be measured in body tissues or blood following exposure to creosote that contains PAHs. Again, these PAH-DNA adducts are not specific for coal-tar creosote, and the adducts measured could have been from exposure to other sources of PAHs.

2.5.2 Biomarkers Used to Characterize Effects Caused by Creosote

The available genotoxicity data indicate that creosote is an indirect mutagen (i.e., requiring the presence of an exogenous mammalian metabolic system) and induces gene mutation in bacteria and mouse lymphoma cells. The mutagenicity of creosote observed in the conventional S. typhimurium assay is at least partially contributed to by the PAHs such as B[a]P and benzanthracene. However, because these results are exclusively from in vitro tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to creosote have been negative, these changes cannot be considered specific biomarkers of effects caused by creosote, nor is it possible to distinguish whether the genotoxic effects result from either acute or chronic exposure to either low or high levels of creosote because all of the data were from in vitro studies. Furthermore, because the mutagenicity of creosote is at least partially due to its PAH components, exposure to PAHs from other sources could produce the same results. Coal-tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues with which it comes in contact. Therefore, burns and irritation of the skin and eyes are the most frequent manifestations of coal-tar creosote toxicity following acute dermal exposure to high levels. However, damage to the skin is not specific to creosote, and can be seen with other corrosive or photosensitizing agents. No other biomarkers (specific or otherwise) have been identified following exposure to creosote.

2.6 INTERACTIONS WITH OTHER CHEMICALS

The primary interactions known to occur between coal-tar creosote and other substances involve the induction of cancer. Coal-tar creosote is a complex mixture of organic substances consisting predominantly of liquid and solid aromatic hydrocarbons. Several of these components of coal-tar creosote are known carcinogens as well as cocarcinogens, initiators, promoters, potentiators, or inhibitors of carcinogenesis. As discussed in Section 2.2.3.8 (Dermal Exposure, Cancer), coal-tar creosote and several of its fractions are carcinogenic when applied to the skin of mice. Dermally applied creosote can also act as a tumor-initiating agent when applied prior to croton oil treatment, and can enhance and accelerate tumor induction by B[a]P. Thus, the risk of cancer following dermal exposure to creosote is likely to be enhanced when concurrent exposure to other potential cocarcinogens, tumor promoters, initiators, and potentiators occurs. Due to the ubiquitous nature of PAHs and other carcinogenic substances in the environment, particularly at hazardous waste sites, the likelihood that these types of synergistic interactions with creosote will occur is good.

Pentachlorophenol and arsenical compounds are also used in wood preserving. For this reason, it is likely that they will be found with creosote at hazardous waste sites. However, there is no information available on the potential interactions of creosote with pentachlorophenol or arsenical compounds.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Data indicate that the population in general may be at increased risk of developing skin cancer following prolonged dermal exposure to creosote. Data also indicate that subsections of the human population may be unusually susceptible to the toxic effects of creosote. These include people with a history of excessive sun exposure, people with skin diseases, and people with exposure to other substances that act as cocarcinogens, tumor promoters, initiators, and potentiators. There is some limited evidence, based on animal studies and the known health effects of the PAH constituents of creosote, that indicates that additional subsections of the population may be susceptible to the toxic effects of creosote. These include fetuses, people with kidney or liver disease, people with deficient immune systems due to disease or advanced age, and people with the genetic trait of inducible aryl hydrocarbon hydroxylase (AHH). AHH is an enzyme contained in the microsomal fraction of the cell that is responsible for the biotransformation of aryl compounds, such as PAHs. When this enzyme is induced, the rate at which aryl compounds are biotransformed into toxic intermediates is increased, rendering these individuals at higher risk. Genetic polymorphism does exist in the general population with regard to the rates of aryl hydrocarbon hydroxylation (i.e., differences in the P-450 and P-448 enzymes).

The results of occupational studies (Henry 1946, 1947), case reports (Cookson 1924; Lenson 1956; O'Donovan 1920), and experimental animal studies (Boutwell and Bosch 1958; Poel and Kammer 1957; Roe et al. 1958) indicate that the general population may be at risk of developing skin cancer following prolonged dermal exposure to creosote. People with skin damaged from excessive sun exposure, disease, or exposure to other substances that potentiate the carcinogenic effect of creosote (Cabot et al. 1984; Lenson

1956; Lijinsky et al. 1956; Sall and Shear 1940) are at an increased risk of developing skin disease, including cancer, from creosote exposure.

Limited evidence from experimental studies of pregnant pigs (Schipper 1961) and pregnant rats (Srivastava et al. 1986) indicate that components of creosote, such as PAHs, cross the placenta following maternal inhalation and may cause fetotoxic effects. Data from a human case report (Bowman et al. 1984) and experimental animal studies (Miyazato et al. 1981, 1984a,b) indicate that kidney or liver disease may increase the risk of developing adverse health effects following ingestion of creosote.

Two other subpopulations may be susceptible to certain components of creosote, such as PAHs; one would be people with deficient immune systems as a result of disease or advanced age, and the second would be people who carry the genetic trait of inducible AHH, one of the mixed-function oxidases. Calabrese (1978) reported that people with deficient immune systems may be at high risk of developing adverse health effects due to exposure to carcinogens, such as PAHs (Stjernsward 1966, 1969; Szakal and Hanna 1972). PAHs are metabolized to reactive intermediates, which are thought to cause cell transformation, mutagenicity, and cytotoxicity. It has been proposed that genetically expressed AHH inducibility is related to the development of bronchogenic carcinoma in persons exposed to PAHs contained in tobacco smoke. Approximately 45% of the general population are considered to be at high risk, and 9% of the 45% are considered to be at very high risk of developing bronchogenic carcinoma following exposure to PAHs (Calabrese 1978). These percentages were estimated from the population frequency of genetically controlled AHH induction (Calabrese 1978).

2.8 ADEQUACY OF THE DATABASE

Section 104(i)5 of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of creosote is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of creosote.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

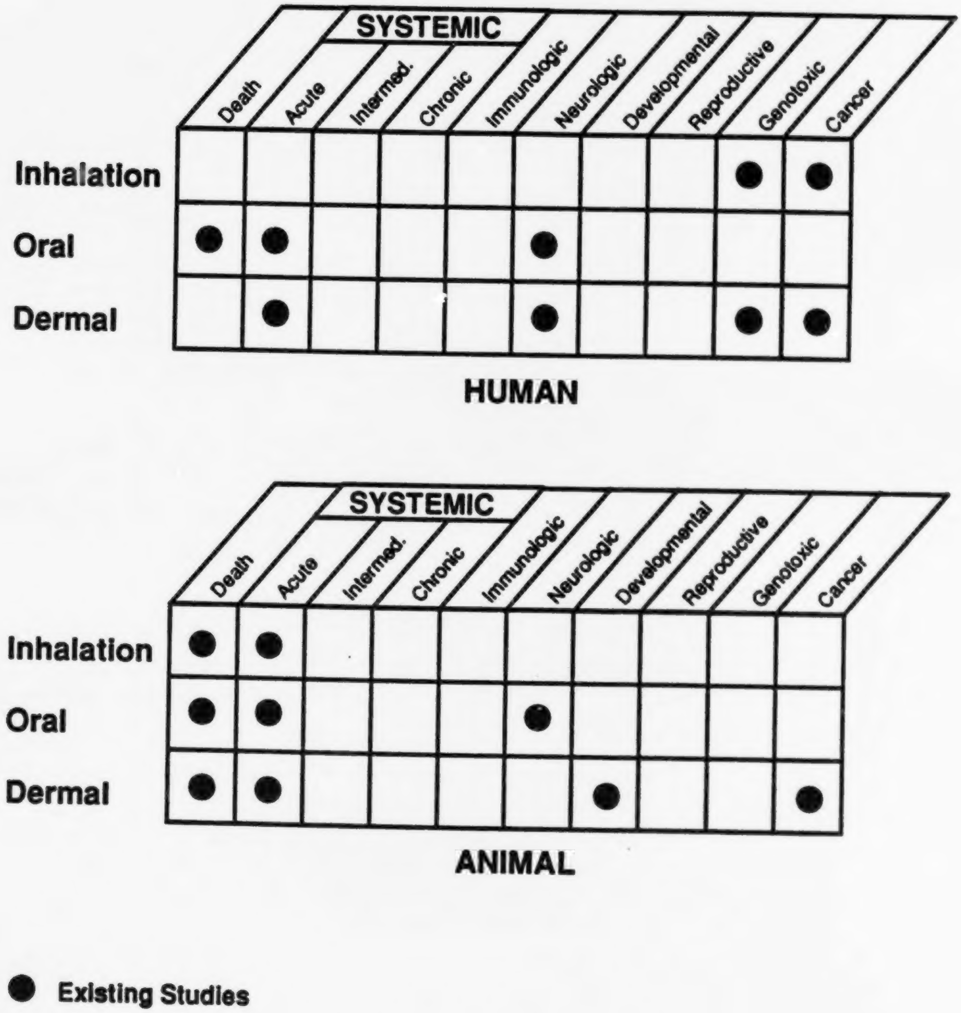
2.8.1 Existing Information on the Health Effects of Creosote

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to creosote are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of creosote. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information. The vast majority of literature reviewed concerning the health effects of coal-tar creosote in humans described case reports of workers exposed predominantly via the dermal route, with a few older reports describing the consequences of accidental or intentional ingestion of creosote. Despite the limitations inherent in these types of studies, an association between dermal exposure to coal-tar creosote and dermal irritation, phototoxicity, and cancer in humans is evident.

The database for the health effects of creosote in experimental animals is lacking, and consists primarily of acute lethality studies or old animal studies that would be considered inadequate by current standards. The systemic effects of ingested creosote have only been well described for beechwood creosote. Little information is available on the effects of creosote following inhalation exposure. However, dermal exposure to coal-tar creosote has been shown in numerous studies to induce skin and lung tumors in mice. Since coal-tar creosote is a complex mixture consisting primarily of PAHs, the toxic effects of coal-tar creosote may be inferred from available information on these constituents. However, given the fact that many of these constituents are known cocarcinogens, initiators, promoters, and potentiators of carcinogenesis, the possibility for the occurrence of synergistic interactions in creosote cannot be ruled out. Thus, information on the toxicity of the various components of coal-tar creosote cannot take the place of sound data on the toxic effects of the creosote mixture itself.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Information is available on the effects of acute-duration exposures to creosote in humans and animals (oral and dermal). The type of information available includes LD_{50}s and acute toxicity in animals (coal-tar and beechwood creosote), and acute toxicity following accidental or intentional ingestion or dermal exposure in humans (coal-tar creosote). Coal-tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues with which it it comes in contact, such as the skin and eyes. Acute ingestion of coal-tar creosote appears to affect primarily the kidney and liver. Thus, the toxic effects of coal-tar creosote on the skin following single-dose dermal exposure in humans are well characterized, but little else is known regarding the systemic effects of this form of creosote in either humans or animals. The available information is



		SYSTEMIC							
	Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation									●	●
Oral	●	●				●				
Dermal		●				●			●	●

HUMAN

		SYSTEMIC							
	Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation	●	●								
Oral	●	●				●				
Dermal	●	●					●			●

ANIMAL

● Existing Studies

FIGURE 2-3. Existing Information on Health Effects of Coal Tar Creosote

insufficient to derive either an acute oral or inhalation MRL for coal-tar creosote because human reports that identified target organs lacked exposure information, and no short-term animal studies exist that describe effects other than death. Identification of target organs from short-term animal studies following oral and dermal exposure would be useful in assessing the risk associated with the acute ingestion or skin contact by humans of coal-tar creosote contaminated water or soils. The pharmacokinetic data on coal-tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Intermediate-Duration Exposure. Information is available on the effects of intermediate-duration dermal exposures to coal-tar creosote in humans and the effects of intermediate-duration exposures to beechwood creosote (oral) and coal-tar creosote (dermal) in animals. The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports rather than controlled epidemiological studies. The animal studies with beechwood creosote describe predominantly hepatic and renal end points, and those conducted with coal-tar creosote describe dermal, but very rarely systemic, effects. Little or no reliable information on respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals is available. The available information is insufficient to derive either an intermediate oral or inhalation MRL for coal-tar creosote because no intermediate-duration animal studies exist that describe effects other than on the skin. Given the widespread use of coal-tar creosote as a wood preservative, and the fact that beechwood creosote is rarely used today, more information on the systemic effects of intermediate-duration exposures to coal-tar creosote by the oral and dermal routes (by conducting 90-day subchronic toxicity studies) would be useful to identify target organs in animals in order to assess the risk associated with the intermediate-duration ingestion or skin contact by humans of coal-tar creosote contaminated water or soils. The pharmacokinetic data on coal-tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Chronic-Duration Exposure and Cancer. Information is available on the effects of chronic-duration dermal exposures to coal-tar creosote in humans and the effects of chronic-duration exposures to beechwood creosote (oral) and coal-tar creosote (dermal) in animals. The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports rather than controlled epidemiological studies. The animal studies with beechwood creosote describe predominantly hepatic and renal end points, and those conducted with coal-tar creosote describe dermal, but very rarely systemic, effects. Little or no reliable information on respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals is available. The available information is insufficient to derive either a chronic oral or inhalation MRL for coal-tar creosote because no chronic-duration animal studies exist that describe effects other than on the skin. Given the widespread use of coal-tar creosote as a wood preservative, and the fact that beechwood creosote is rarely used today, more information on the systemic effects of chronic-duration exposures to coal-tar creosote by the oral and dermal routes would be useful to identify target organs in animals in order to assess the risk associated with the chronic-duration ingestion or skin contact by humans of coal-tar creosote contaminated water or soils. The pharmacokinetic data on coal-tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Various older case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote exposure with the development of skin cancer. However, several newer studies are available that suggest that there is no association between exposure to creosote or other coal-tar products and cancer in humans. Several skin painting studies have been conducted in animals using coal-tar creosote and its various fractions. Although many of these studies would be considered inadequate by current standards, the results nevertheless indicate that coal-tar creosote and its constituents can induce skin tumors as well as act as tumor initiators and promoters. Although carcinogenicity studies have been conducted with beechwood creosote by the oral route, the relevance of the findings to coal-tar creosote is not known. More information on the carcinogenic potential of chronically ingested coal-tar creosote (e.g., an oral bioassay) would be useful. The pharmacokinetic data on coal-tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., skin tumors following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Genotoxicity. The genotoxic potential of coal-tar creosote has been investigated almost exclusively using in vitro assays. The limited genotoxicity tests that have been conducted on urine obtained from humans exposed to creosote have been negative. The available data indicate that creosote is an indirect mutagen and induces gene mutation in bacteria and mouse lymphoma cells. However, a substantial database exists on the genotoxic effects of the PAHs found in the creosote mixture. More in vivo assays with creosote would be useful to more completely characterize the genotoxic potential of the creosote mixture.

Reproductive Toxicity. No information on the reproductive effects of coal-tar creosote in humans or animals is available. However, limited data available on benzo(a)pyrene indicate that this PAH has a potential to induce adverse reproductive effects. An increase in relative testis weight was observed in rats administered beechwood creosote in the diet for 3 months. There were no accompanying gross or histopathological lesions of the testes in these animals, so the toxicological significance of this change is not known. Given the widespread potential for exposure to coal-tar creosote, and the indication that certain PAH components of coal-tar creosote as well as beechwood creosote may be reproductive toxicants, reproductive organ pathology should be examined in any 90-day studies that may be conducted. If these preliminary data indicate that creosote may present a reproductive hazard, then multi-generation reproductive toxicity studies should be conducted by the oral and dermal routes of exposure. The pharmacokinetic data on coal-tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., skin tumors following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Developmental Toxicity. Information on the developmental effects of creosote in humans was not found. Data from one severely limited study in pigs indicate that coal-tar creosote has the potential to be fetotoxic. Limited information available on a few PAHs (mostly benzo[a]pyrene) indicate that ingested PAHs have a potential to induce adverse developmental effects in animals. Given the widespread potential for exposure to coal-tar creosote, and the suggestive data mentioned above, oral and dermal developmental toxicity studies in animals would be useful to assess the potential risk for creosote-induced adverse developmental effects. The pharmacokinetic data on coal-tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., skin tumors following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Immunotoxicity. The only available information on the immunological effects of creosote describes the occurrence of acute allergic dermatitis following exposure to creosote bush resin. The relevance of these findings to exposure to coal-tar creosote is not known. However, since creosote bush resin and coal-tar creosote do contain some similar constituents (e.g., phenolic derivatives), and people with deficient immune systems may be at high risk of developing adverse health effects due to exposure to carcinogens, such as the PAHs contained in creosote, more information on the immunologic effects of dermally applied coal-tar creosote would be useful to better characterize the toxic effects of exposure to coal-tar creosote. Preliminary information on the potential for creosote to induce immunotoxic effects may be obtained from 90-day studies that examine effects on lymphoid tissue and blood components. If adverse effects on these parameters are observed, then a full battery of immunotoxic tests may be warranted to further characterize the potential immunotoxicity of creosote.

Neurotoxicity. The available information describes neurological involvement in humans and animals following short-term high-level oral exposure to creosote (both beechwood and coal-tar). These effects are generally excitatory in nature (i.e., convulsions). No information is available on the long-term neurotoxic effects of low-level exposure to coal-tar creosote in humans and animals. Long-term neurotoxicity studies in animals, using sensitive functional and neuropathological tests, would be useful in determining if coal-tar creosote is a neurotoxic agent.

Epidemiological and Human Dosimetry Studies. Few controlled epidemiological studies have been conducted in humans on the effects of exposure to coal-tar creosote. In particular, epidemiological studies of workers in creosote treatment plants would be useful to more fully assess the risk of inhalation and dermal exposure to coal-tar creosote. Most of the available information on the effects of coal-tar creosote in humans comes from cases of acute poisoning following the accidental or intentional exposure to coal-tar creosote and from occupational exposures in the wood-preserving and construction industries. Limitations inherent in these studies include unquantified exposure concentrations and durations, as well as concomitant exposure to other potentially toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow-up periods, and brief exposure periods. Despite their inadequacies, studies in humans suggest that coal-tar creosote is a dermal irritant and a carcinogen following dermal exposure. Well-controlled epidemiological studies of people living in close proximity to areas where coal-tar creosote has been detected in surface and groundwater, near hazardous waste sites, and of people occupationally exposed could add to and clarify the existing database on creosote-induced human health effects. Particular effects to be examined include cancer (of the skin and other organs) and other adverse skin effects.

Biomarkers of Exposure and Effect. No method is currently available to measure the parent creosote mixture in human tissues or fluids. However, the PAH components of the creosote mixture and their metabolites (e.g., 1-hydroxypyrene) can be measured in the urine of exposed individuals following relatively high-level exposures of acute and chronic duration. The identification of PAH metabolites in the urine could serve as a method of biological monitoring of exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where creosote has been detected. However, because of the ubiquitous nature of PAHs in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to creosote. PAH exposure can occur from a variety of sources, and there is no way to determine if creosote was the source. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to creosote containing PAHs. Again, these PAH-DNA adducts are not specific for coal-tar creosote, and the adducts measured could have been from exposure to other sources of PAHs. Therefore, a biomarker of exposure specific to creosote would be useful to monitor exposure to this mixture.

The formation of benzo(a)pyrene-DNA adducts has been demonstrated and may also serve as a biomarker of PAH-induced carcinogenicity. However, these adducts are not specific for coal-tar creosote exposure, as exposure to benzo(a)pyrene from sources other than coal-tar creosote can occur. Studies to identify and measure effects more diagnostic of coal-tar creosote-specific injury would be useful. Also, increasing the sensitivity of these tests would be valuable in evaluating the health status of individuals who have been exposed to low levels of creosote.

Absorption, Distribution, Metabolism, and Excretion. Studies monitoring the pharmacokinetics of the coal-tar creosote mixture are limited. Much of the information regarding the disposition of creosote is based on indirect evidence or the pharmacokinetic information available on a single class of components of creosote, the PAHs.

Absorption of creosote occurs following all routes of exposure. The presence of creosote components in tissues and the presence of metabolites in urine were evidence of its absorption. However, no studies are available that quantify the extent and rate of creosote absorption.

Studies in humans or animals regarding the distribution of creosote are not available. Its distribution is based on assumptions derived from studies that monitored the distribution of PAHs, components of creosote.

The metabolism of creosote has not been extensively studied, but preliminary results indicate that hydroxylation of the major PAH components is a principal degradation pathway in both humans and animals following all routes of exposure. 1-Hydroxypyrene is one metabolite that has been identified, but there were no studies available regarding the identification of other metabolites. Elucidation of additional biotransformation pathways and products is also important in examining potential toxic effects of creosote. Moreover, no studies were located regarding the rate or extent of creosote metabolism.

Studies regarding the excretion of creosote by humans or animals were not available. It is known that PAHs and their metabolites are primarily excreted in the bile and the feces. However, direct excretion studies with creosote would be more useful. Information is available regarding the disposition of creosote's individual components, but no information is available regarding how these components interact to affect the overall disposition.

In summary, no data are available regarding the toxicokinetics of the creosote mixture and all information must currently be inferred from what is known about the PAH components of creosote. Interactions between the components of the creosote mixture could occur that could alter the rate and extent of absorption, distribution, metabolism, and excretion of creosote from what might be predicted based on what is known about the individual PAH components. Therefore, more information on the toxicokinetics of the creosote mixture itself would be useful to predict possible target organs of toxicity as well as allow for extrapolation of toxic effects across routes of exposure.

Comparative Toxicokinetics. The available information indicates that the absorption, distribution, metabolism, and excretion of creosote is qualitatively similar in humans and rodents. This general conclusion was primarily based on evidence derived from studies on the individual PAH components of creosote. Detailed pharmacokinetic studies in humans and animals specific to the creosote mixture would provide a better indication of species differences and indicate whether the ability to extrapolate across species may be possible in the future.

2.8.3 On-going Studies

Creosote is currently subject to an EPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration standard and data call-in, and the Creosote Council II is planning to conduct a research program that includes testing in subchronic inhalation, subchronic dermal, developmental, and reproductive toxicity.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical synonyms and identification numbers for coal-tar creosote are listed in Table 3-1. Creosote is a complex mixture of variable composition containing primarily aromatic ring compounds and condensed aromatic ring compounds. Therefore, it is not possible to represent the chemical formula and structure of the creosote mixture.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of coal-tar creosote are listed in Table 3-2.

Coal-tar creosote is defined by the American Wood Preserver's Association (1988) as:

> A distillate derived from coal-tar. As used in the wood preserving industry, creosote denotes a distillate of coal-tar produced by the high temperature carbonization of bituminous coal. Creosote consists principally of liquid and solid aromatic hydrocarbons and contains some tar acids and tar bases; it is heavier than water and has a continuous boiling range beginning at about 200°C.

It is thus a complex mixture typically composed of 85% PAHs and 2%-17% phenolics (Bedient et al. 1984). The composition of the mixture may also vary across lots and across manufacturers. The major PAH components of creosote are listed in Table 3-3 . Creosote is further classified according to a set of standards regarding physical property specifications for creosote that must be met for certain types of creosote. The physical property specifications for the different types of creosote are listed in Table 3-4. Type P1/P13 creosote is a straight creosote distillate and is used in ground contact, land, and fresh and marine water applications. Type P2 creosote is used by the railroad industry in the treatment of railroad crossties.

Coal-tar itself is produced by the carbonization, or coking of coal. Coal-tar is defined by Hawley (1977) as:

> A black, viscous liquid (or semi-solid), naphthalene-like odor, sharp burning taste; obtained by the destructive distillation of bituminous coal, as in coke ovens; 1 ton of coal yields 8.8 gallons of coal-tar. Combustible. Specific gravity 1.18-1.23 (66/60°F). Soluble in ether, benzene, carbon disulfide, chloroform; partially soluble in alcohol, acetone, methanol, and benzene; only slightly soluble in water.

To distinguish another product of coal-tar from creosote, coal-tar neutral oils are usually defined as a mixture of naphthalene, fluorene, anthracene, and other neutral hydrocarbons (Smale, 1977). Neutral hydrocarbons consist of those coal-tar hydrocarbons other than coal-tar acids (such as phenols, cresols, and cresylic acids), and coal-tar bases (such as pyridines, quinolines, and acridines).

Because of the variability in feedstock and manufacturing processes, presentation of exact values for various properties presented in Table 3-2 are not possible.

TABLE 3-1. **Chemical Identity of Coal-tar Creosote**

	Value	Reference
Chemical name	Coal-tar creosote	AWPA 1988
Synonyms	Creosote Oil, Dead Oil, Brick Oil, Coal-tar Oil, Creosote P1, Heavy Oil, Liquid Pitch Oil, Wash Oil	Windholz 1983; Weiss 1986; HSDB 1988
Trade Names	Preserv-O-Sote	HSDB 1988
Chemical Formula	No data[a]	Windholz 1983 HSDB 1988
Chemical Structure	No data[a]	
Wiswesser Line Notation	UVCB	HSDB 1988
Identification Numbers:		
CAS Registry	8001-58-9	Weiss 1986
NIOSH RTECS	GF8615000	HSDB 1988
EPA Hazardous Waste	U051	HSDB 1988
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	DOT: 1933; IMCO: 3.2; IMCO/UN: 9/1993	Weiss 1986
HSDB	6299	HSDB 1988
NCI	No data	

[a] Creosote is a mixed compound composed primarily of polycyclic aromatic hydrocarbons including phenanthrene, acenaphthene, fluorene, anthracene, and pyridine.

AWPA = American Wood Preservers' Association
CAS = Chemical Abstracts Service
NIOSH = National Institute for Occupational Safety and Health
RTECS = Registry of Toxic Effects of Chemical Substances
DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code
HSDB = Hazardous Substances Data Bank

TABLE 3-2. Physical and Chemical Properties of Coal-Tar Creosote

Property	Value	Reference
Molecular weight	No data	
Color	Translucent amber to brown to black liquid	Windholz 1983
Physical state	Liquid	Weiss 1988
Melting point	No data	
Boiling point	>180° C	Weiss 1986
	194-400° C	HSDB 1988
Density (g/cm3)	1.07 (20° C)	DOT 1985
Odor	Sharp odor	Windholz 1983
	Tarry, aromatic odor	Weiss 1986
	Smoky odor	HSDB 1988
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water	Practically insoluble	Windholz 1983
Organic solvents	Miscible with alcohol, ether, fixed or volatile oils	HSDB 1988
Partition coefficients	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition Temperature	335° C	Windholz 1983
Flashpoint	75° C	Windholz 1983
Flammability limits	1.3-8%	HSDB 1988

TABLE 3-3. Major Chemical Components of Typical Wood Preservative Creosote*

Component	Percent P1/P13 Creosote**	P2 Creosote
Indene	3.3	0.5
Methylbenzofurans and xylenol	1.0	
Naphthalene	14.3	8.7
Quinoline	0.9	0.7
2-Methylnaphthalene and indole	4.9	5.6
1-Methylnaphthalene	2.1	2.1
Biphenyl	1.3	1.5
Dimethylnaphthalenes	2.1	
Acenapthylene	0.8	
Acenaphthene	4.1	4.9
Dibenzofuran	3.5	3.4
Fluorene	4.7	4.5
Methyldibenzofurans	3.0	
Methylfluorenes	2.2	0.8
Dibenzothiophene	0.9	
Phenanthrene	12.7	16.9
Anthracene	5.6	5.3
Benzoquinolines	0.8	
Carbazole	0.9	2.2
2-& 3-Methylphenanthrenes	2.0	3.0
Fluoranthene	6.0	7.3
Pyrene	5.0	6.5
Benzofluorenes and methylfluoranthenes	3.0	
Methylpyrenes	1.9	
Chrysene	1.5	3.5
Methylchrysene and benzanthracenes	1.0	1.1

*These values are calculated averages which are representative of creosote. Actual concentrations of specific constitutents can vary. Naphthalene, for example, can range from five to twenty percent.

**See Table 3-4 for the physical property specifications for each type of creosote.

Source: Butala 1990

TABLE 3-4. Physical Property Specifications for Various Types of Creosote

	Range of Properties	
Typical Physical Properties	Creosote Distillate (P1/P13)	Creosote/ Coal-tar Solution (P2)
Water, Percent by Volume	0.0–0.7	0.2-0.13
Specific Gravity at 38°C:		
Whole Fraction	1.059-1.102	1.083-1.121
235/315 Fraction	1.034-1.044	1.033-1.042
315/355 Fraction	1.098-1.125	1.094-1.122
Xylene Insoluble, Percent by Weight	0.06-0.40	0.80–1.90
Distillation, Percent by Weight		
to 210°C	0.0–0.9	0.9–1.1
to 235°C	3.0–10.0	1.6–6.6
to 270°C	15.0–35.6	13.8–36.9
to 315°C	43.4–58.0	37.6–54.2
to 355°C	70.0–76.6	60.0–71.1
Residue	23.7–27.5	27.4–40.0

Source: Butala (1990)

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Creosote refers to one of three complex mixtures of organic compounds. One mixture is derived from coal-tar (CAS Registry number 8001-58-9), one is produced from wood (e.g., beechwood) (CAS Registry number 8021-39-4), and the third is derived from the resin of the creosote bush (Larrea). Coal-tar creosote is produced from a distillation of coal-tar produced by high-temperature carbonization. Because coal-tar is a by-product of steel manufacturing, domestic production of coal-tar products is dependent on demand for steel (USITC 1987). Creosote production falls into two categories: distillate (100% creosote), and creosote in coal-tar solution. Annual production and sales figures for the years 1950 through 1987 are listed in Table 4-1. Distillate production in 1986 was 46.8 million gallons; creosote in solution was 31.6 million gallons (USITC 1987). Distillate production in 1987 was 47.3 million gallons. Production of creosote in solution in 1987 was not disclosed, but solution sales in 1987 were 34.3 million gallons (USITC 1988). The following organizations manufacture creosote domestically: Allied Corp, Morristown, New Jersey; Coopers Creek Chemical Corp, West Conshohocken, Pennsylvania; Koppers Co., Pittsburgh, Pennsylvania; Reilly Industries, Inc., Indianapolis, Indiana; Aristech Chemical Corp., Gary, Indiana; U.S. Steel Corp , Pittsburgh, Pennsylvania; Witco Chemical Corp., Woodcliff Lake, New Jersey; Crowley Tar Products Co., New York, New York; Los Angeles Chemical Co., South Gate, California; and Standard Tar Products Co., Milwaukee, Wisconsin (USITC 1988; HSDB 1988).

4.2 IMPORT

In 1984, 7.3 million gallons of creosote were imported into the U.S. (Bureau of Census 1984a), and 7.5 million gallons were exported from the U.S. (Bureau of Census 1984b). The is the most current data available regarding the import and export of creosote.

4.3 USE

Coal-tar creosote was used as a wood preservative in the United States for over 100 years. Wood preservation accounts for over 97% of current coal-tar creosote production (Santodonato 1985). Coal-tar creosote is applied to wood by commercial pressure treatment or by home and farm dipping or brushing, although this latter use is not significant since creosote is now a restricted use pesticide (EPA 1986b). Coal-tar creosote is a wood preservative and

Table 4-1. U.S. Production of Creosote Oil[a]

Year	Creosote in Coal-Tar Solution[b] (100% creosote basis) (millions of gallons)		Distillate[b] (100% creosote basis)[c] (millions of gallons)	
1987	47.3		----	(34.3)
1986	46.8	(31.5)	31.6	(36.6)
1985	64.3	(40.0)	66.6	(42.3)
1984	42.2	(30.4)	40.8	(30.9)
1983	39.5	(24.7)	40.9	(27.7)
1982	36.3	(21.4)	44.3	(32.2)
1981	81.0	(61.5)	61.1	(44.5)
1980	60.6	(37.1)	----	
1979	80.5	(40.5)	27.2	(10.9)
1978	51.3	(36.3)	35.0	(26.3)
1977	47.0	(35.4)	36.0	(25.2)
1976	77.1	(51.9)	36.8	(26.4)
1975	79.2	(50.7)	35.7	(35.2)
1970	103.4		25.6	
1965	111.1		12.5	
1960	82.0		10.8	
1955	106.1		16.4	
1950	106.7		35.6	

[a] Source: Santodonato 1985; USITC 1987, 1988.

[b] Figures in parentheses are sales figures.

[c] Figures for 1982 and 1981 only are 100% solution basis.

water-proofing agent for railroad ties, telephone poles, marine pilings, and fence posts. In addition, coal-tar creosote prevents animals and vegetable growth on concrete marine pilings, and is a component of roofing pitch, fuel oil, and lamp black and a lubricant for die molds (HSDB 1988). Other uses include animal and bird repellent, insecticide, animal dip, and fungicide (IARC 1985).

Beechwood creosote and its compounds calcium creosotate, creosote carbonate, and creosote valerate were used in the past as antiseptics and expectorants (Windholz 1983). Treatments for leprosy (Samson and Limkako 1923), pneumonia (McKinlay 1933), and tuberculosis (Fellows 1939a) also involved ingestion of beechwood creosote. Beechwood creosote is rarely used for medicinal purposes today.

4.4 DISPOSAL

Creosote sludge generated from coal-tar creosote production can be fixed, solidified, and covered with clay in the settling lagoon used in treatment. This "disposal in place" requires groundwater monitoring for a 30-year period (Ball et al. 1985). Due to RCRA Land Disposal Restrictions, creosote can no longer be disposed in hazardous waste landfills unless treated to EPA-specified treatment standards (EPA 1990). Industrially used creosote-treated wood can be burned in an industrial incinerator or boiler (EPA 1986b). Treated wood used in the home or farm should be buried or disposed with household garbage, it should not be incinerated (American Wood Preservers Institute 1988).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Creosote is a complex commercial mixture of some 300 organic constituents. The composition of the mixture varies from batch to batch depending on the coking process used. Creosote consists primarily of PAHs, and therefore the fate of much of the components of the mixture is similar to that of PAHs. The primary releases of creosote to the environment are in wastewater effluents from wood-treatment plants. Compared to releases to surface water and soil, creosote releases to the atmosphere are considered to be insignificant. Creosote has been found in at least 31 of the 1177 hazardous waste sites on the NPL (VIEW Database 1989). The frequency of these sites within the United States can be seen in Figure 5-1. Biotransformation by microbes is the primary process by which creosote constituents are degraded in soils, surface waters, and groundwater. The mixture is relatively stable and persistent in the environment; half-life data are not available.

Creosote has been widely used as a wood-treatment pesticide since the turn of the century. As a result of this widespread and long-term use, workers in the wood-preserving industry have been exposed to creosote for many years. Human exposure to creosote can occur by inhalation or direct dermal contact. Individuals working in wood-preserving facilities are one of the largest exposed groups. Exposure may also occur during handling and installation of treated wood products in structures such as bridges, piers, retaining walls, crossties, and fencing; as a result of burning treated scrap wood; and through contact with contaminated media at hazardous waste sites. The general public is unlikely to experience any significant exposure to liquid creosote through the direct use of wood preservative products because EPA canceled all nonwood uses of the material and restricted use of creosote products to certified applicators in January 1986 (EPA 1986b).

5.2 RELEASES TO THE ENVIRONMENT

There are no known natural sources of the creosote mixture (IARC 1973). However, several of the PAH constituents of the mixture are known to have natural sources; the reader is referred to the ATSDR Toxicological Profile for PAHs (ATSDR 1990) for additional information on natural sources, releases, and levels of PAHs not associated with creosote production, use, and disposal.

The major source of creosote released to the environment is wastewater effluents from wood treatment facilities (USDA 1980). Companies that preserve wood with creosote may treat their aqueous wastes in on-site biological treatment plants or release the wastewater into a municipal water treatment system (EPA 1978; von Rumker et al. 1975). Some creosote components may also be released to the atmosphere by fugitive emissions from these facilities.

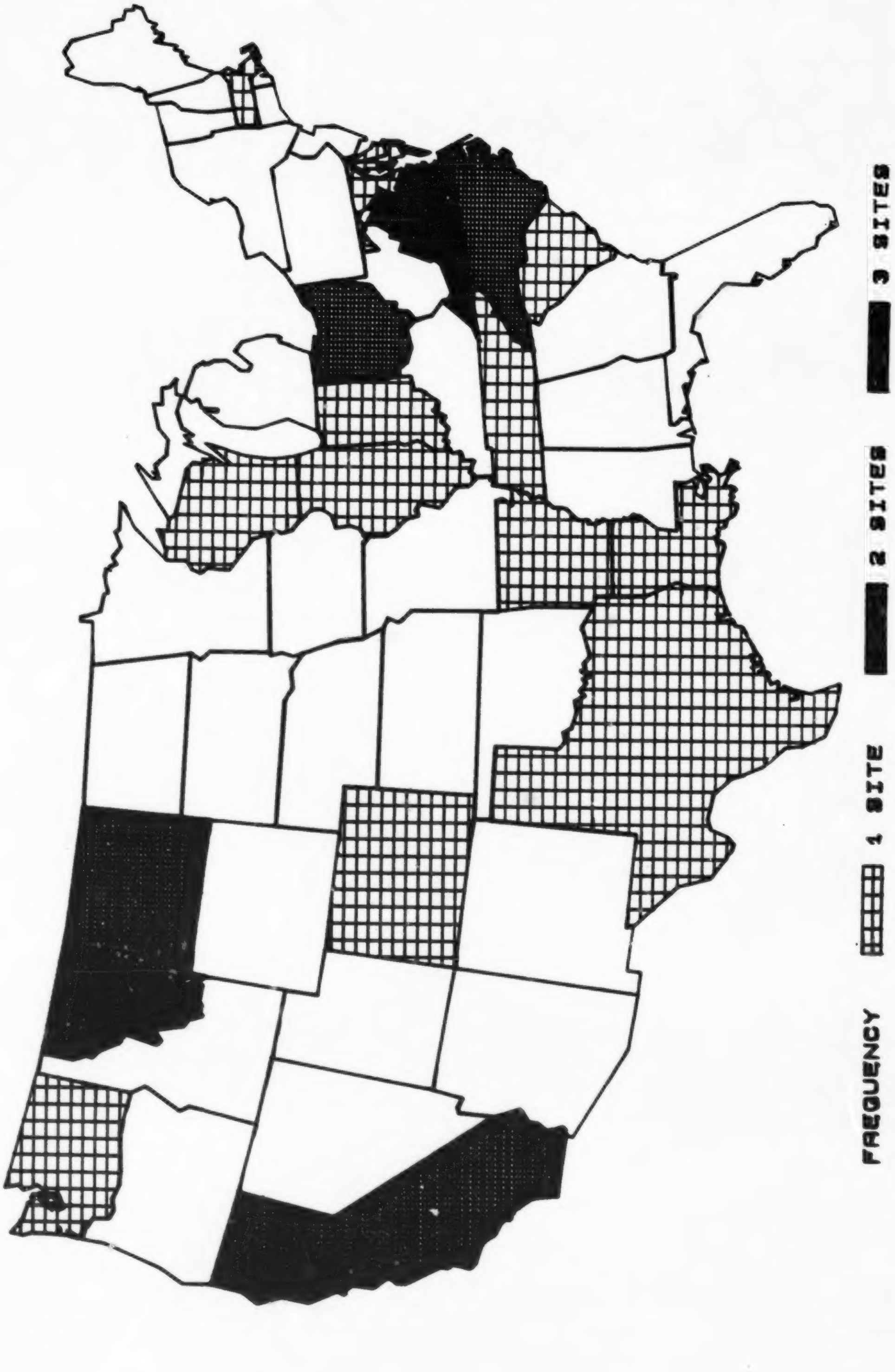

FREQUENCY
1 SITE
2 SITES
3 SITES

FIGURE 5-1. FREQUENCY OF SITES WITH CREOSOTE CONTAMINATION

However, atmospheric releases are considered to be minimal in relation to releases in wastewaters.

Creosote components may also be slowly released from the surface of treated wood products by oil exudation, leaching by rainwater, or volatilization. Losses of creosote from impregnated wood are dependent on the kind of coal used to produce the coal-tar, the kind of coke oven used to make the coal-tar and the conditions under which the wood is used (Leach and Weinert 1976).

5.2.1 Air

Atmospheric releases of creosote from wood-preserving plants are not well defined. Creosote constituents such as naphthalene, acenaphthylene, acenaphthene, phenanthrene, and fluorene have been detected in emissions at a pressure treatment facility that treated logs for use as utility poles and marine pilings (Engineering Science 1986). Releases may occur at several points in the treatment process, such as when cylinder doors are opened after a treatment cycle, or when creosote is transferred from the heater to the cylinder at the beginning of the impregnation process. Atmospheric releases vary from plant to plant, depending on the process design, and are considered to be significantly smaller than releases to surface water in aqueous effluents (Henningsson 1983).

On a hot, sunny day evaporation of creosote from the surface of treated wood may release creosote constituents to the atmosphere. Only the volatile creosote components such as acenaphthene and naphthalene will volatilize; the heavier fractions will remain on the wood (USDA 1980).

In a terrestrial microcosm study, release of ^{14}C-labeled creosote components to the atmosphere from treated wood accounted for 1.0% of total acenaphthene and 1.4% phenanthrene whereas 93.5% and 95% of these components, respectively were retained in the wood (Gile et al. 1982).

Other potential sources of atmospheric releases include incineration of scrap wood treated with the mixture and re-entrainment of dust and soils contaminated with components of the mixture in the vicinity of hazardous waste sites.

5.2.2 Water

The major source of creosote released into surface waters and groundwater is wastewater effluents from wood-preserving facilities (USDA 1980). In previous years, wastewater generated from wood treatment facilities was often discharged to unlined evaporation/settling lagoons where a sludge was formed. Water-soluble creosote components then percolated through the soil to reach the groundwater table. Wastewaters may include process water generated from steam conditioning of the wood, preservative formulation recovery and regeneration water, water used to wash excess preservative from the surface of the wood, condensate from drying kilns used to dry preserved or surface-protected wood, water that accumulates in door and retort sumps, and rain falling on or in the immediate vicinity of the treating cylinder and work tank area. Groundwater contamination from creosote wastewaters and sludge stored in unlined surface water impoundments at a wood treatment facility has been reported in Pensacola, Florida (Goerlitz et al. 1985). Similar contamination problems have been reported in Conroe, Texas (Borden 1986), and St. Louis Park, Minnesota (Hickock et al. 1982).

Water-soluble creosote constituents (e.g., phenols) may be released to surface water or groundwater by leaching from the surface of creosote contaminated soils at hazardous waste sites or from treated wood products coming into contact with water, such as marine pilings. For example, some studies have shown that creosote is lost to a greater extent from marine timber than from timber placed in freshwater as a result of cell contraction caused by the high concentration of salts in seawater (Henningsson 1983).

5.2.3 Soil

Creosote may be released to soils at treatment facilities as a result of bleeding of the product from treated timber in stock yard and storage areas and through disposal of the mixture at hazardous waste sites. Rain water may also wash the soluble components directly from the surface of treated timber and into the soil (Henningsson 1983).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Creosote constituents released to surface waters will differentially partition to the water column or to sediments depending on their water solubility and sorptive properties. For example, PAHs, the major constituents of creosote, generally tend to sorb strongly to soil and sediment particulates and have low aqueous solubilities and mobility (Hickock et al. 1982). Nitrogenous bases present in creosote wastewater (e.g., aniline, toluidines, and xylidines) are relatively soluble, mobile, and persistent in groundwater (Pereira et al. 1983). However, behavior at a given site is also dependent on site-specific characteristics. For example, PAH, phenol, and heterocyclic components of creosote wood treatment process wastes were found to migrate en masse in groundwater through a contaminated sand and gravel aquifer in Pensacola, Florida; sorption of these different classes of organic constituents in the low organic carbon(<0.1%) aquifer materials was not important (Pereira and Rostad 1986).

In an investigation of the extent of creosote contamination at four wood preservative plants with process water surface impoundments, unspecified creosote components were found to have moved 20-60 feet vertically from the impoundments to the water table and up to 500 feet horizontally from the sources (Ball 1987).

In an investigation of the release of creosote from treated wood into freshwater and sea water, naphthalene, phenanthrene, acenaphthene, dibenzofuran, fluorene, and 2-methylnaphthalene were found to be the major components that migrated into water (Ingram et al. 1982). The rate of migration was found to increase significantly with increasing temperature within the range of 20° to 40°C and occurred more slowly from aged than from freshly treated pilings.

In a terrestrial microcosm study, 2.7% of radiolabeled phenanthrene and 4.3% of radiolabeled acenaphthene were found in soil samples taken in a 10-cm zone around creosote-treated posts, whereas concentrations of the compounds in the posts were 95% and 93.5% of the amounts applied, respectively, after 2.5 months (Gile et al. 1982).

Limited uptake of some creosote constituents has been detected in plants exposed to creosote-treated wood in nearby soil. Only 0.04% of applied acenaphthene and 0.1% of phenanthrene partitioned to plants in one study (Gile et al. 1982).

Animals such as voles, crickets, snails, pill bugs, and worms have exhibited the capacity to assimilate radiolabeled creosote components in terrestrial microcosm studies. Creosote components were found to accumulate to the greatest extent in the vole, with bioconcentration factors of 12-31. The ^{14}C mass balance content of the animals was 1.2% of applied acenaphthene and 0.8% of applied phenanthrene versus 4.3% and 2.7%, respectively, in soils (Gile et al. 1982). In addition, mussels taken from creosote-treated pilings have been found to contain significantly more B[a]P, a creosote constituent, than those growing elsewhere (Dunn and Stich 1976). Accumulation of creosote-derived PAHs has been reported in benthic organisms in Pensacola Bay (Elder and Dresler 1988; Rostad and Pereira 1987). Fluoranthene, pyrene, B[a]P, anthracene, chrysene, and phenanthrene were detected in higher concentrations in tissues of snails (Thais haemastoma) and oysters (Crassostrea virginica) taken from offshore sites near an onshore wood treatment plant than from control sites.

5.3.2 Transformation and Degradation

5.3.2.1 Air

No information was found in the available literature concerning the transformation of creosote components in the atmosphere.

5.3.2.2 Water

Creosote components are degraded in aquatic environments by microfaunal metabolism (Borthwick and Patrick 1982; Ingram et al. 1982). Microorganisms may act on the creosote-treated wood itself or on creosote components that have leached from the treated wood. Quinoline, the major tar base in creosote, has been reported to be degraded in surface water and groundwater by bacteria of the genus Pseudomonas (Bennett et al. 1985). Biotransformation of the phenolic components of creosote apparently also occurs under anaerobic conditions in contaminated groundwater (Ehrlich et al. 1983; Goerlitz et al. 1985). Adaptation of soil microorganisms to PAH contaminants in groundwater originating from creosote treatment plant wastes has also been reported (Wilson et al. 1986).

Creosote components have been detected in surface water samples taken near a wood-treatment facility that ceased operation 30 years earlier (Black 1982). The creosote appeared to have been transported through the soil and was entering the river via seepages and springs. Weathering processes produced only minor constitutive changes in the creosote with relative losses of the lower molecular weight components. These changes probably reflected the greater volatility and solubilities of the two and three carbon ring PAHs.

5.3.2.3 Soil

Creosote components are slowly released from treated wood products by oil exudation, rainwater leaching, and by volatilization of the lighter fractions (Henningsson 1983). USDA (1980) reported that the major components of creosote were not detected in soil samples taken to a depth of 6 inches within 2-24 inches from treated poles, presumably as a result of biotransformation of mobilized components by soil microorganisms. Creosote components released to soils in wastewater effluents have been found to be biotransformed by soil microbes under aerobic conditions (Middleton 1984). Bacteria of the genus Pseudomonas isolated from a creosote-contaminated waste site have been reported to degrade creosote-derived quinoline (Bennett et al. 1985). Acclimation to creosote phenolic constituents by soil microorganisms has also been demonstrated (Smith et al. 1985).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No information was found in the available literature regarding ambient atmospheric concentrations of creosote-derived components (i.e., PAHs) in the United States. Workplace air concentration data are discussed in Section 5.5. Data on ambient atmospheric concentrations of PAHs derived from other sources can be found in the ATSDR Toxicological Profile for PAHs (ATSDR 1990).

5.4.2 Water

Results from 2 years of groundwater sampling at an abandoned wood treatment facility in Conroe, Texas where creosote had been used for about 20 years showed that wells were contaminated with levels of up to 3490 μg/L naphthalene, 1263 μg/L methylnaphthalene, 425 μg/L dibenzofuran, and 302 μg/L fluorene. The contaminants had apparently migrated through the clay and sand soils on the site from three waste pits (Bedient et al. 1984).

5.4.3 Soil

Several PAH constituents of creosote were detected in soil samples taken at an abandoned wood treatment facility in Conroe, Texas at depths of up to 25 feet. Maximum concentrations of the compounds were detected in samples collected at the 0.7-1.8 ft depth. Maximum concentration levels were 3.7 mg/kg for naphthalene, 3.4 mg/kg for methylnaphthalene, 3.8 mg/kg for dibenzofuran, 4.2 mg/kg for fluorene, and 2.2 mg/kg for anthracene (Bedient et al. 1984).

5.4.4 Other Media

Creosote-derived phenanthrene, 1,2-benzanthracene, and B[a]P have been detected in river sediments at concentrations of up to 231,000 μg/kg, 62,000 μg/kg, and 16,000 μg/kg, respectively, downstream from the site of a former wood treatment facility (Black 1982). Creosote-derived PAHs were also detected in the sediments of Pensacola Bay and a drainage stream in the vicinity of a former wood treatment facility near Pensacola, Florida. PAH concentrations ranged from 200 μg/g for naphthalene to 140,000 μg/kg for anthracene in stream sediments; concentrations in Pensacola Bay ranged from 75 μg/kg for benzanthracene to 190 μg/kg for fluoranthene (Elder and Dresler 1988).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Individuals working in the wood-preserving industry comprise the largest portion of the population potentially exposed to creosote. Workers employed at creosote pressure treatment facilities may be exposed by direct dermal contact or by inhalation of volatilized components. Approximately 4,000 workers in the United States were employed at 188 pressure treatment plants that used creosote as a preservative in the late 1970s (USDA 1980). Potential exposure to creosote in these plants is minimized by the use of closed systems for receiving, transferring, mixing, storing, and applying the mixture to wood products. Similarly, dermal exposure from the handling of freshly treated wood is minimized by the use of highly mechanized processes. Exposure via inhalation, however, is more likely to occur. For example, worker exposure may be significant during opening of treatment cylinder doors and cylinder cleaning operations (EPA 1981b). Inhalation and dermal exposure are also more likely in plants using nonpressure treatment methods such as thermal and dip treatments in open tanks. An estimated 100 workers were involved in commercial thermal and dip treatment operations in the late 1970s. Some of these workers experienced consistently high inhalation exposures (USDA 1980). Other historical nonpressure treatment exposures included an estimated 50,000 individuals (e.g., homeowners, farmers, landscapers) who applied creosote in noncommercial brush, dip, spray, and soak treatments (EPA 1981a). Dermal contact and inhalation may have resulted in exposure to high concentrations of creosote components for these individuals, but the exposures were usually of intermittent frequency (USDA 1980). However, designation of creosote products as restricted use pesticides by EPA in 1986 has probably decreased the number of individuals potentially exposed in these nonpressure wood treatment applications (EPA 1986b).

There are currently 25,000 workers employed in about 75-100 domestic wood treatment plants using creosote. As a result of the use of engineering controls and personal protective equipment (e.g., respiratory protection and impervious gloves) required in the 1986 settlement of the EPA Special Review process[2], airborne exposures to creosote components in the workplace are generally below the OSHA permissible exposure limit (PEL) of 0.2 mg benzene soluble particulates/m^3 air (Rivers 1990).

However, prior to the standard use of these controls by industry, workers were potentially exposed to higher airborne concentrations of creosote constituents. For example, the concentration of creosote (i.e., coal-tar pitch volatiles) components in personal air samples taken at a railroad tie treatment facility in Somerville, Texas, were found to range from 0.003 to 1.211 mg/m^3 (Todd and Timbie 1980). Another industrial hygiene survey of worker exposure to creosote at a wood-treatment facility in Tacoma, Washington, showed coal-tar pitch volatiles in personal air samples ranged from less than 0.4 μg/m3 to 111.9 μg/m3 (Todd and Timbie 1981). The higher concentrations were found at the end of the treatment process when the cylinder was opened. NIOSH investigated creosote exposure among dock builders in Brooklyn, New York, in 1980. Employees were reported to have substantial direct skin contact with creosote. Breathing zone concentrations of the cyclohexane extractable fraction of the coal-tar pitch volatiles ranged from zero to 0.059 mg/m3 of air (Baker and Fannick 1981). Monitoring data collected from 11 creosote treatment facilities in the United States showed that worker breathing zone concentrations of benzene-soluble particulates averaged 0.07 mg/m^3 (range 0.01–0.061 mg/m^3) (EPA 1981a). Comprehensive studies of worker exposure to creosote in wood treatment plants have been conducted by Koppers Company alone and in conjunction with NIOSH (SRI International 1977; Markel et al. 1977). Data from these studies indicated that, on the average, employee exposure to particulate polycyclic organic materials (PPOM) was within the permissible level of 0.1 mg/m^3 recommended by NIOSH for coal-tar volatiles. The only components that could be reliably measured in the vapor-phase fractions collected were naphthalene, methylnaphthalene, and acenaphthene. The concentrations of these chemicals ranged from 0.54 to 2.0 mg/m^3. Fluorene and phenanthrene-anthracene were detected in trace quantities but were not quantifiable. Benzene-soluble particulates (PPOM) ranged from 0.02 to 0.10 mg/m^3.

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[2] A Special Review of a currently registered pesticide may be initiated by EPA when validated data indicate that certain types of toxicity (e.g., carcinogenicity, developmental toxicity, acute effects) exist for humans or for non-target plant or animal species. A formal process exists for notifying registrants and other interested parties, requesting further data regarding the pesticide in question, analyzing and reporting risks and benefits, and requesting public review. The final regulatory decision may be implemented over a period of time or it may be imposed immediately as an emergency action based solely on the EPA's finding of immediate danger to human health or the environment.

A gravimetric analytical method has been used in most of these workplace monitoring studies. This method involves the collection of airborne particulates on glass fiber filters and subsequent extraction by solvents, such as benzene or cyclohexane. The extracted fraction of the particulate matter is determined by weighing. As a result of two significant shortcomings of this method, the inability to identify constituents of the airborne particulates and to sample vapor phase components, EPA (1981a) concluded that definitive information was not available on the identity of airborne components of creosote in workplace atmospheres. EPA (1981a) also stated that quantitative estimates of treatment plant worker dermal exposures and quantitative inhalation or dermal exposure data for workers applying creosote in nonpressure treatment scenarios and for downstream workers who install, handle, or contact treated wood products were unavailable. Vapor phase components were found to be an important source of worker exposure in an industrial hygiene survey of wood treatment facilities conducted in Finland. Most of the airborne contaminants in worker breathing zones were in the vapor phase; the proportion of particulate PAHs to total concentration of vapors was <0.5%-3.7% (Heikkila et al. 1987).

Exposure to creosote may also occur during installation of treated poles, during inspection and maintenance operations, and through casual contact (USDA 1980). One of the major end point uses of creosote is treatment of railroad crossties. Since crossties are installed mechanically by railroad companies, workers generally have minimal dermal exposure in this process. Exposure via inhalation, however, is considered to be moderate and consistent during this type of installation procedure. In other situations, crossties may be installed manually, in which case there is consistent moderate to high exposure via skin contact as well as by inhalation. The amount of exposure via skin contact ranges from moderate to high depending on whether workers wear protective clothing. Skin contact is considered minimal for railroad personnel who inspect ties in service as well as for the general public who may have casual contact with creosote-treated crossties. In instances where crossties are used for landscaping purposes, contractors involved in the sale and installation of freshly treated ties experience consistent moderate exposure via inhalation and minimal to occasionally high exposure for skin contact.

Installation of treated lumber and timbers in structures such as bridges, piers, retaining walls, fences, and barns involves a significant amount of manual contact. Likewise, the installation of switch ties, cross planks, crossarms, block flooring, and fence posts is usually done manually. In these situations, human exposure via inhalation is considered moderate while exposure via skin contact may vary from minimal to high depending on the type of protective equipment used (USDA 1980).

The opportunity for direct dermal contact is particularly high for workers installing treated poles. Activities such as attaching fittings often preclude the use of protective gloves, and as a result of creosote bleeding from the treated poles, the potential for dermal contact of workers performing maintenance operations persists for years after installation (Henningsson 1983).

Exposure of individuals installing treated fence posts and lumber and timbers via inhalation of creosote volatiles (e.g., acenaphthene and naphthalene) can also occur when freshly treated materials are handled under calm, hot, sunny conditions (USDA 1980).

Potential sources of non-occupational human exposure to creosote include contact with creosote-treated wood products (e.g., railroad ties used for landscaping), incineration of creosote-treated scrap lumber, and contact with contaminated environmental media at hazardous waste sites (e.g., ingestion of contaminated groundwater). Direct exposure of homeowners to wood treatment products containing creosote should be limited, since EPA has restricted the sale and use of such products to certified applicators. Industrial sources have noted that there have been no reports or instances of health effects allegations, except for rare reports of skin irritation, resulting from public contact with creosote-treated wood in the last 20 years.

The only information on biological indicators of exposure to creosote found in the available literature involved a study of 1-hydroxypyrene in the urine of a creosote wood treatment plant worker (Jongeneelen et al. 1985).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals living in the vicinity of hazardous waste sites and abandoned wood treatment plants contaminated with creosote may experience higher levels of exposure than the rest of the general population.

Individuals who apply creosote directly to wood, including farmers, carpenters, and homeowners who come in contact with creosote-treated wood products are believed to be exposed to the highest levels of creosote components via inhalation and dermal contact. It has been estimated that historically about 4,000 workers may have been routinely exposed and up to 50,000 people may have been intermittently exposed to creosote through its application as a preservative to wood products (USDA 1980). The size of this population has probably decreased over the last few years since EPA restricted the use of creosote to certified applicators.

5.7 ADEQUACY OF THE DATABASE

Section 104(i) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of creosote is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of creosote.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. Limited physical property data, such as boiling point and density (see Table 3-2), are available for the coal-tar creosote mixture. Additional physical and chemical property data, such as water solubility, vapor pressure, K_{oc}, and Henry's law constant values would be useful in order to predict the partitioning and transformation of coal-tar creosote components in air, water, and soil. These values are currently not available because their determination is complicated by the fact that creosote is a mixture of variable composition.

Production, Use, Release, and Disposal. Manufacturing methods are well described in the literature. Production figures are limited because of the confidential nature of this business information. Uses of creosote, both coal-tar and beechwood, are well described. Since the use of coal-tar creosote as a wood preservative has been restricted, the potential of the population to be exposed is greatly diminished. The major releases of creosote resulting from treatment processes at wood-preserving plants are known but the levels are not well quantified. Current production, release, and disposal information would assist in identifying the levels of creosote present in the environment and, thus, populations potentially exposed as a result of these processes. Creosote sludge from production processes can be treated and disposed on-site with proper groundwater monitoring. Creosote can no longer be disposed in hazardous waste landfills unless treated to EPA-specified standards. Creosote-treated wood used in industrial applicators can be burned in an industrial incinerator or boiler; however, treated wood used in domestic or farm applications should be buried rather than incinerated.

Environmental Fate. The limited information available regarding transport and partitioning of creosote components among environmental compartments indicates mobility of PAH, phenol, and heterocyclic constituents of the mixture in water, sorption of PAH components in soils, and bioconcentration of creosote-derived PAHs by terrestrial and aquatic organisms. Biotransformation appears to be the most important degradation process in soils and aquatic environments. Additional data on the transport of volatile creosote components in the atmosphere and the partitioning of creosote released to surface waters and soils would be useful. Quantitative data on the rates of biotransformation in soils, surface water, and groundwater under aerobic and anaerobic conditions would also be useful. The importance of other transformation processes, such as photolysis, photooxidation, and hydrolysis, in relation to biotransformation and rates of transport between media, should also be defined. These data would be useful to help define potential pathways of human exposure and to estimate ambient concentrations of creosote components in environmental media.

Bioavailability from Environmental Media. Very limited information was found in the available literature regarding the uptake of creosote components by living organisms from contaminated water and soil at hazardous waste sites. Studies have been done with persistent constituents (e.g., PAHs) which show that plant uptake from soils is limited, whereas bioconcentration in aquatic organisms from contaminated surface waters has been demonstrated. Data from human and animal studies indicate that creosote components are absorbed following ingestion, inhalation, and dermal exposure to the mixture. PAH and phenol constituents have also been demonstrated to be absorbed following exposure by these routes. However, quantitative information regarding the uptake and bioavailability of creosote from contaminated environmental media is not available. In addition, data are needed on the bioavailability of creosote components following ingestion of creosote-contaminated soils.

Food Chain Bioaccumulation. Very limited information was found in the available literature regarding the biomagnification of creosote-derived compounds among food chain trophic levels. However, PAHs, the major persistent constituents of the commercial mixture, have not been reported to undergo significant biomagnification in aquatic food chains because of the ability of many aquatic organisms to rapidly metabolize and eliminate these compounds (Eisler 1987). Since components of the mixture are not concentrated to high levels in human food items, food chain bioaccumulation does not appear to be an important source of human exposure and no additional information is needed at this time.

Exposure Levels in Environmental Media. Limited information is available regarding ambient concentrations of creosote-derived PAHs in soils and no data are available regarding atmospheric concentrations of creosote components. Very limited information is available on concentrations of component compounds in surface waters and sediments receiving wood treatment plant effluents. Data are particularly lacking for contaminated media in the vicinity of hazardous waste sites. These data would be useful to estimate the exposure of populations coming into contact with components of the mixture through inhalation of contaminated air, consumption of contaminated surface water or groundwater, or direct dermal contact with environmental media.

Exposure Levels in Humans. A population exists that is potentially exposed to creosote through contact with contaminated media at hazardous waste sites and with treated wood products. A second potentially exposed workforce population exists at wood treatment facilities. Currently no information exists that demonstrates tissue levels of any components of the mixture in these populations. Estimates of human exposure to creosote constituents, or body burdens of creosote components, are complicated by the lack of information on exposure to creosote constituents and levels of creosote-derived components in the environment. Collecting information on tissue levels of creosote components in humans would be necessary to examine the relationship between levels of creosote-derived compounds in the environment, human tissue levels, and subsequent development of health effects.

Exposure Registries. No exposure registries for creosote were located. This compound is not currently one of the compounds for which a subregistry has been established in the ATSDR National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the ATSDR National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

Creosote is currently subject to a FIFRA registration standard and data call-in by EPA. In addition, the Creosote Council II is planning to conduct a research program that includes testing for worker exposure and protection.

Remedial investigation/feasibility studies being conducted at the 31 NPL sites where creosote has been found and at the numerous creosote-contaminated RCRA corrective action sites should provide data on concentrations of the mixture in contaminated media in the vicinity of hazardous waste sites. For example, creosote constituents have been found in surface water impoundments and soil samples taken near wood treatment facility sites in Colorado, Louisiana, Texas, and Montana.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring creosote mixtures in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify the components of creosote. Rather, the intention is to identify well-established methods that are used as the standard methods of analyses. Many of the analytical methods used to detect creosote mixtures in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

The analytical methods used to quantify creosote mixtures in biological and environmental samples are summarized below. Table 6-1 lists the applicable analytical methods for determining components of creosote in biological fluids and tissues and Table 6-2 lists the applicable analytical methods for determining the components of creosote in environmental samples.

6.1 BIOLOGICAL MATERIALS

Coal-tar creosote contains a highly complex mixture of organic components. These include PAHs (polycyclic aromatic hydrocarbons), phenols, sulfur, oxygen and nitrogen heterocycles. Various PAHs have been found to constitute about 85% of coal-tar creosote (Bedient et al. 1984). The levels of creosote in biological materials can therefore be estimated by measuring the PAH content in biological samples. The methods available to measure PAHs in biological materials include gas chromatography equipped with a flame ionization detection (GC/FID), gas chromatography coupled to a mass spectrometry (GC/MS) and high performance liquid chromatography (HPLC). Immunoassay techniques, i.e., enzyme linked immunosorbent assays (ELISA) and ultrasensitive enzyme radio immunoassay (USERIA), ^{32}P-postlabeling and synchronous luminesence spectroscopy (SLS) are methods currently being developed to detect and quantify ultratrace levels of PAH adducts bound covalently to macromolecules (e.g., DNA).

GC/MS and HPLC has been employed to detect creosote-derived PAH complexes at ppt (pg/g) levels in human tissues (Liao et al. 1988; Obana et al. 1981). The detection and quantification of trace levels of PAHs in biological tissues involves extensive and rigorous clean-up procedures including florisil, silica and alumina column chromatography (Liao et al. 1988; Obana et al. 1981).

TABLE 6-1. Analytical Methods for Determining Creosote-Derived PAH Components in Biological Materials

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Adipose tissues	Add 8% benzene in hexane to adipose tissue sample and homogenize; add Na_2O_4, stir and load onto florisil column; elute column with 8% benzene in hexane, concentrate, and analyze	GC/MS	5-50 ng/g	52%-95% recovery	Liao et al. 1988
Liver	Add S-9 mix (KH_2PO_4 buffer, $MgCl_2$, KCl, glucose-6-phosphate, $NADP^+$) at pH 7.4 to homogenized sample in DMSO and incubate with shaking at 37°C; add ice-cold acetone to stop reaction and extract with ethyl acetate; dry (Na_2SO_4), concentrate, and analyze metabolites	HPLC	No data	No data	Amin et al. 1982
	Mince tissue sample, saponify with KOH/EtOH, and extract with hexane; separate hexane layer and extract with DMSO; pour DMSO layer into 15% aqueous NaCl solution and reextract with hexane; wash hexane layer with water, dry (Na_2SO_4), and concentrate; load extract onto silica or alumina gel column; elute column with hexane followed by diethyl ether:hexane (15:85) and concentrate eluent	HPLC	0.006-0.46 ng/g	No data	Obana et al. 1981
Blood	Collect blood sample in heparinized plastic tube and centrifuge; separate white blood cells and isolate DNA by standard RNase and phenol treatment; assay BPDE-NDA adduct by immunoassay	ELISA	$1x10^{-15}$ mol BPDE per μg DNA	No data	Perera et al. 1988
	Isolate PAH-DNA adduct from white blood cells of blood; digest adduct with radiolabeled (^{32}P)ATP; resolve the radiolabeled adducts on TLC plate and detect by counting radioactivity	^{32}P-Postlabeling	$0.3x10^{-15}$ mol adduct per μg DNA	No data	Philips et al. 1988
	Collect blood sample in heparinized plastic tube and centrifuge; collect lymphocyte cells and isolate BPDE-DNA adduct by standard treatment; analyze BPDE-DNA adduct by immunoassay and SLS	ELISA or USERIA and SLS	0.006-$0.23x10^{-15}$ mol BPDE per μg DNA	No data	Harris et al. 1985

TABLE 6-1 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Urine	Inject animal with radiolabeled benzo(a)pyrene; collect urine sample, add MeOH and load onto C-18 Sep-Pak Column; elute with aqueous MeOH and analyze eluent by HPLC	HPLC	5×10^{-12} mol 7-BPDE-Gua per µg of labeled benzo(a) pyrene	No data	Autrup and Seremet 1986

GC/MS = gas chromatography/mass spectrometry; HPLC = high performance liquid chromatography; ELISA = enzyme linked immunosorbent assay; USERIA = ultra-sensitive enzyme radioimmunoassay; SLS = synchronous luminescence spectroscopy; NADP$^+$ = oxidized nicotinamide adenosine dinucleotide; DMSO = dimethyl sulfoxide; BPDE = benzo(a)pyrene diol epoxide; and Gua = guanine.

TABLE 6-2. Analytical Methods for Determining Creosote-Derived PAH Components in Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Wooden sleepers (railroad crossties) in play ground	Extract accurately weighed sample with diethylether; filter extract through anhydrous sodium sulfate and evaporate the solvent; perform acid/base/neutral liquid-liquid separations on creosote residue	GC/MS	1-3 ng/sample	No data	Rotard and Mailahn 1987
Coal-tar creosote	Dissolve sample in cyclohexane and extract with 90% methanol; evaporate extract to dryness; dissolve residue with cyclohexane and extract with nitromethane; evaporate extract to dryness and dissolve residue with small amount of benzene	GC	10 ppm	No data	Lijinsky et al. 1963
	Dissolve sample in methylene chloride at a concentration of ~10% ($^w/_w$); inject sample solution into g.c. for analysis	GC	No data	No data	Nestler 1974
River sediments	Digest wet sediment sample in boiling EtOH/KOH; partitioned hydrocarbons by extraction into cyclohexane; concentrate extract and load onto florisil column; elute PAH complex from column with 50% methylene chloride/hexane; concentrate sample and analyze	HPLC	No data	No data	Black 1982
Contaminated groundwater	Filter sample through prebaked glass-fiber filters to remove suspended sediments; pass sample through a bonded-phase extraction column; elute trapped organic compound from column with acetonitrile followed by methylene chloride; dry elute with Na_2SO_4 and concentrate with a stream of dry nitrogen	GC/MS	50 μg/L	95% recovery	Rostad et al. 1984
Impregnated wood (work-place)	Heat sample at 60·C in a chamber and load onto an XAD-2 resin column; extract resin with diethyl ether and analyze	GC/MS	0.01-0.005 mg/m^3	82%-102% recovery	Heikkila et al. 1987

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
	Collect heated sample on a prewashed (cyclohexane) glass fiber filter; extract sample with cyclohexane and evaporate to dryness; dissolve residue in acetonitrile: water (85:15)	HPLC	8 ng/m^3	No data	Heikkila et al. 1987
Creosote treated wood	Place a small piece of treated wood in a solid sample holder in the heated injection port of G.C.; vaporize the creosote from wood onto column and analyze	GC	No data	No data	Lorenz and Gjovik 1972
Gas and particulate matter (workplace)	Pump sample through a glass fiber filter-amberlite XAD-2 adsorbent sampling system; extract with diethylether in an ultrasonic bath; concentrate ether extract and dilute with acetonitrile and analyze	HPLC	0.005 to 2.5 mg/m^3	87%-102% recovery	Anderson et al. 1983

GC/MS = gas chromatography/mass spectrometry; GC = gas chromatography; HPLC = high-performance liquid chromatography; and PAH = polycyclic aromatic hydrocarbon.

6. ANALYTICAL METHODS

There is considerable evidence that PAHs are enzymatically converted to highly reactive metabolites that bind covalently to macromolecules such as DNA, thereby causing carcinogenesis and mutagenesis in mammalian systems. Thus, benzo(a)pyrene a prototype of the carcinogenic PAHs and the most thoroughly studied PAH, is converted by specific cellular enzymes to the syn- and anti-isomers of 7β, 8δ-dihydroxy-(9δ, 10δ)-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BPDE) and binds covalently to DNA, resulting in formation of the putative BPDE-DNA adduct (Harris et al. 1985; Haugen et al. 1986; Autrup and Seremet 1986).

The ELISA technique has been employed for detecting antibodies in serum bound to BPDE-DNA adducts. The USERIA method involves measuring the immunological response of BPDE-DNA in the presence of rabbit anti-serum, alkaline phosphatase enzyme and radiolabeled para-nitrophenyl phosphate (PNPP). The radioactivity of the hydrolysed tritiated PNPP is measured by a scintillation counter. Both ELISA and USERIA methods has been employed to detect PAH-DNA adducts at 10^{-15} mol levels in the blood and tissues of humans occupationally exposed to PAH (Amin 1982; Harris et al. 1985; Haugen et al. 1986; Newman et al. 1988; Perera et al. 1988). The ^{32}P-postlabeling method involves a 5'-labeling of DNA adducts that has been digested with nuclease P_1 enzyme system to 3'-mononucleotides. Adducts present in the digest that were resistant to nuclease P_1 were thus labeled with ^{32}P, while unmodified nucleotides were not. The digested DNA adducts are separated by thin-layer chromatography and quantified by scintillation counting. A detection limit of 0.3×10^{-15} mol of PAH adduct per μg of DNA (less than one adduct in 10^7 nucleotides) has been achieved (Philips et al. 1988).

6.2 ENVIRONMENTAL SAMPLES

Coal-tar creosote is a amber to brown oily liquid obtained by the fractional distillation (at 200°–400°C) of crude coal-tars. The commercial product is a highly complex mixture of hundreds of components, including PAHs, phenols, and nitrogen, oxygen, and sulfur heterocycles. The mixture per se cannot be measured. The PAH component fraction is most often used as an indicator of creosote contamination of environmental media. For example, screening for total PAHs is often used at hazardous waste sites when creosote contamination is suspected. The PAH fraction is used in these analyses because it is more persistent than the phenolic fraction, which tends to be more mobile and biodegradable. The methods used to measure total PAHs also detect the nitrogen, oxygen, and sulfur heterocyclic components of the mixture.

The determination of trace amounts of creosote-derived PAHs in environmental samples has been restricted to a limited number of techniques. These include high-performance liquid chromatography (HPLC), gas chromatography equipped with flame ionization detection (GC/FID), and gas chromatography coupled to chemical ionized mass spectrometer (GC/MS).

6. ANALYTICAL METHODS

GC/FID or GC/MS are perhaps the most widely employed analytical techniques for the determination of creosote-derived PAHs in coal-tar, contaminated groundwater, wooden sleepers (railroad crossties), and impregnated wood (Heikkila et al. 1987; Lijinsky et al. 1963; Lorenz and Gjovik 1972; Nestler 1974; Rotard and Mailahn 1987; Rostad et al. 1984). GC/FID is one of the methods recommended by EPA for detection of PAHs in wastewater and solid waste (EPA 1986c).

Heikkila et al. (1987), employed GC/MS technique to determine creosote levels of impregnated wood in the workplace. Detection limits of 10×10^{-6} to 50×10^{-6} g of creosote per m^3 of sample and recoveries of 82% and 102% were achieved. Heikkila and co-workers measured the components of PAHs with a reverse phase HPLC equipped with fluorescence detection. For the detection of creosote vapors, naphthalene was used as an indicator since it constitutes about 18% by weight of total PAHs in creosote (Andersson et al. 1983; Heikkila et al. 1987). Rotard and Mailahn (1987) used a modified sample extraction procedure to identify various components of creosote extracts in wooden sleepers. The procedure involved the separation of compounds by functional group using acid, base, and neutral conditions. Detected compounds include phenanthrene, anthracene, and naphthalene (neutral extractions), quinoline and isoquinoline (basic extraction), cresols, and phenols (acidic extraction). Rostad and co-workers (1984) developed a method for isolation and detection of creosote in contaminated groundwater. This method involves passing the sample through a small column containing a solid-bonded phase adsorbent, which adsorbs the organic compounds. The authors indicated that this method is simple, faster, and cheaper to perform than the acid/base/neutral extraction procedure. It effectively isolated all organic compounds from contaminated groundwater regardless of polarity, functional group, or water solubility in one step, thereby minimizing hazardous exposure to sample.

HPLC equipped with fluorescence detection has been used to identify creosote-derived PAH complex in river sediments (Black 1982). Complex peaks of PAH compounds were observed using an excited wavelength at 300 nm and an emitted wavelength at 420 nm. Some PAHs, such as phenanthrene and B[a]P, were completely resolved using appropriate chromatographic conditions. Benz[a]anthracene was only partially resolved (absorbance at 254 nm) from a complex of peaks associated with the chrysene-benzene[a]anthracene doublet (Black 1982). Andersson et al. (1983) employed an amberlite XAD-2 adsorbent instead of filter system for isolating organic compounds from gas and particulate matter in creosote impregnating plant. Good sample recoveries and a detection limit of 5×10^{-6} g of creosote per m^3 of sample were achieved. HPLC, with either fluorescence or UV detection, is an EPA-recommended method for the analysis of both solid and liquid hazardous waste (EPA, 1986c). At present, HPLC does not achieve the high detection capability of capillary gas chromatography. HPLC however, does offer some advantages for the determination of creosote-derived PAH complex in environmental samples. Firstly, HPLC offers a variety of stationary phases capable of providing unique selectivity for the separation of PAH isomers that are often difficult to separate by GC. Secondly, ultraviolet absorption and fluorescence detection provide sensitive and more importantly, selective detection of PAHs in HPLC technique.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)5 of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of creosote is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of creosote.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Creosote is a complex mixture of organic compounds and no methods exist for measuring the parent compound in biological media. However, sensitive methods do exist for measuring components of the creosote mixture. Most of these methods involve detection of PAHs, the predominate components of creosote, and their metabolites. These analytical methods can reliably detect trace levels of PAHs in human tissues and body fluids, making them sensitive enough to measure background levels in the population, as well as levels at which biological effects might occur. PAHs, however, are not unique to creosote exposure. Development of analytical methods sensitive and selective enough to measure possibly unique or unusual components of creosote, or capable of yielding a unique "fingerprint" for the compound, would be useful in monitoring exposures that might occur in work environments and near hazardous waste sites where creosote has been detected.

The analytical methods for measuring PAHs and their metabolites in biological tissues and fluids are sensitive enough to measure levels at which health effects might occur, as well as background levels in the population. Methods also exist for measuring PAH-DNA adducts, and research efforts are underway to develop methods that will detect ultratrace levels of these adducts in biological media. The increased sensitivity may allow correlation between levels of these adducts and observed health effects of creosote-related PAH exposure. There is also a need for methods to quantitatively correlate monitored levels of various PAHs in biological tissues or fluids to toxic effects in humans. Methods dependent on monitoring PAHs, however, are not specific for creosote exposure. Methods sensitive and selective enough to detect a more unique component or group of components making up the creosote mixture would allow a more accurate assessment of the health effects associated with exposure to monitored levels of creosote.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Reliable and sensitive methods are available for measuring PAHs from creosote in soil, water, air, and other environmental media. Exposure to creosote is most likely to occur in industrial settings where creosote is manufactured or used. Creosote-contaminated water and soil are a concern in areas near hazardous waste sites and other areas where creosote might be concentrated. The analytical methods available are accurate and sensitive enough to quantitatively detect PAHs in these and other environmental media, and are effective for estimating creosote levels in media known to be contaminated with this compound. There is a lack of sensitive reliable methods for detecting and measuring creosote degradation products in environmental media. Development of such methods would allow assessment of the possible health effects of exposure to creosote metabolites and assist in determining the level of potential exposure to these products.

6.3.2 On-going Studies

No on-going studies concerning techniques for measuring and determining creosote in biological and environmental samples were reported.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and advisories pertaining to creosote in air, water, and food are summarized in Table 7-1. Regulations and advisories pertaining to the components of creosote (i.e., PAHs and phenol) can be found in the ATSDR Toxicological Profiles for these chemicals (ATSDR 1989b, 1990). Creosote is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987b).

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the toxicological profiles.

Adsorption Coefficient (Koc) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

9. GLOSSARY

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (Kow) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

9. GLOSSARY

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX

PEER REVIEW

A peer review panel was assembled for creosote. The panel consisted of the following members: Dr. David Strayer, Health Science Center, University of Texas; Dr. Paul Mushak, Private Consultant, Durham, NC; and Dr. Rick Irvin, TEES Engineering Toxicology Division, Texas A&M University. These experts collectively have knowledge of creosote's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.